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VOLUME XXXIV NUMBER 4

DISEASES

of the

CHEST

OFFICIAL PUBLICATION

PUBLISHED MONTHLY

OCTOBER
1958

PUBLICATION OFFICE, CHICAGO, ILLINOIS

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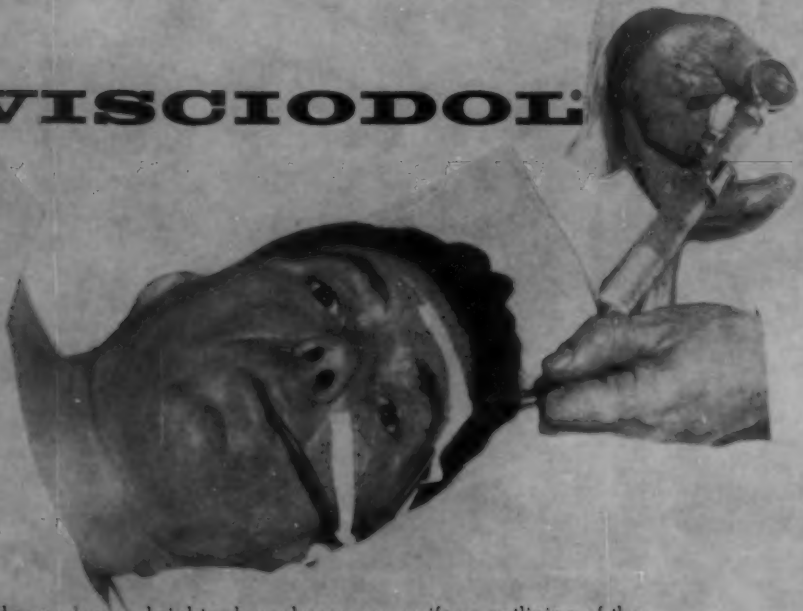

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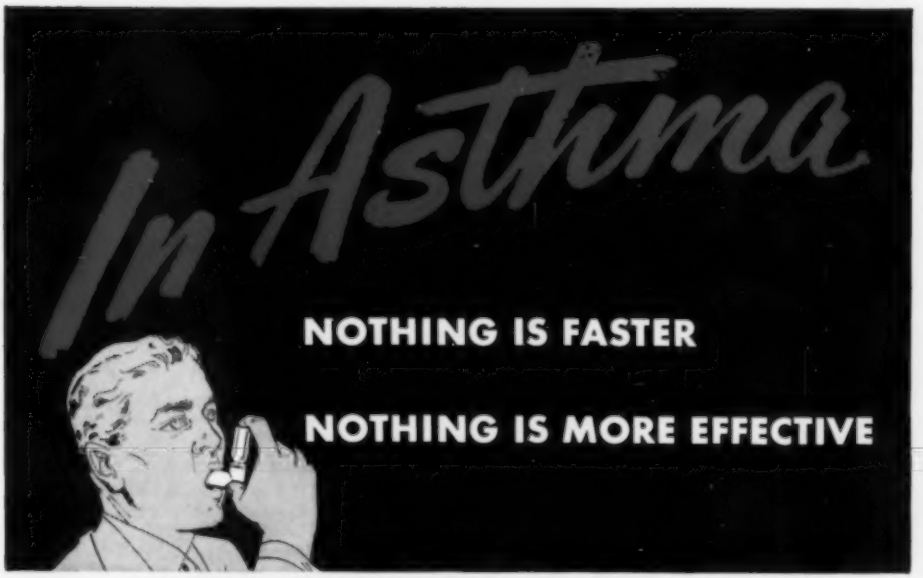

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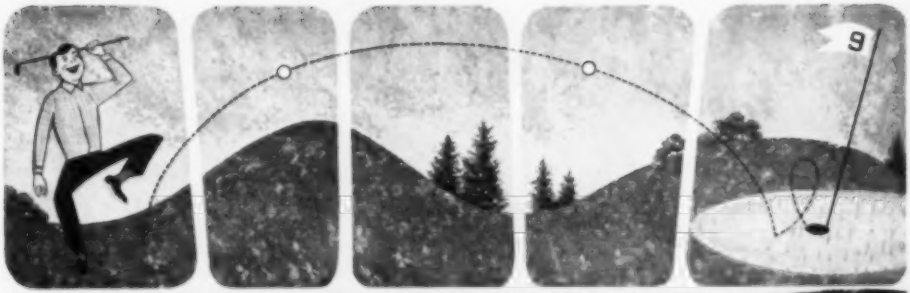

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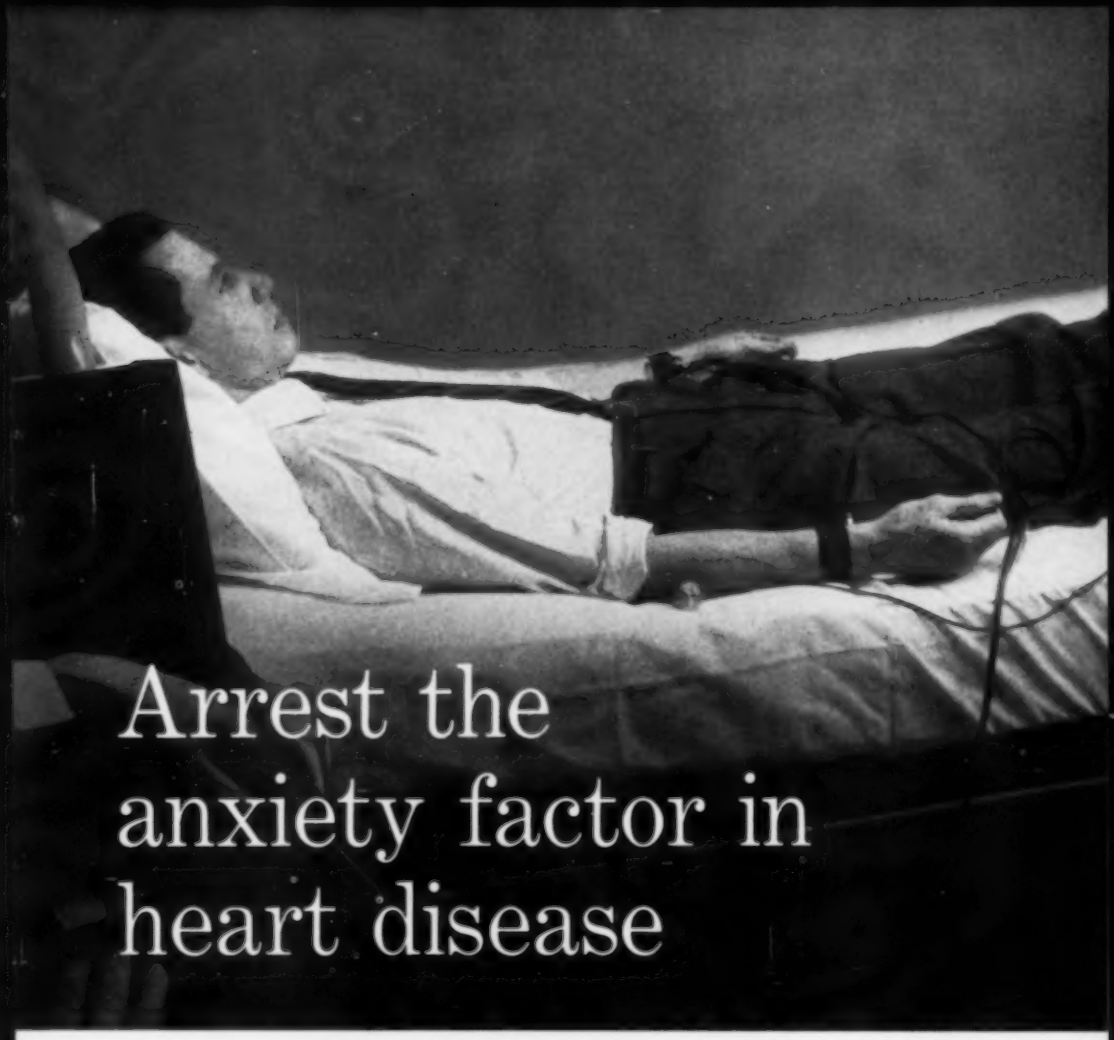

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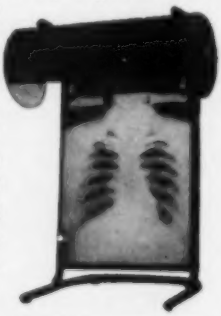

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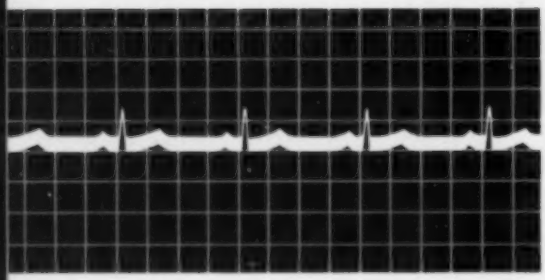

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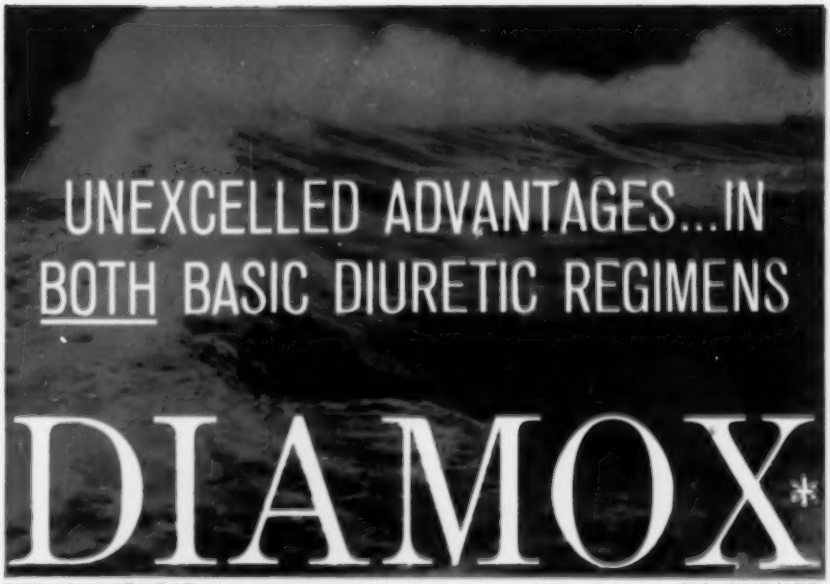

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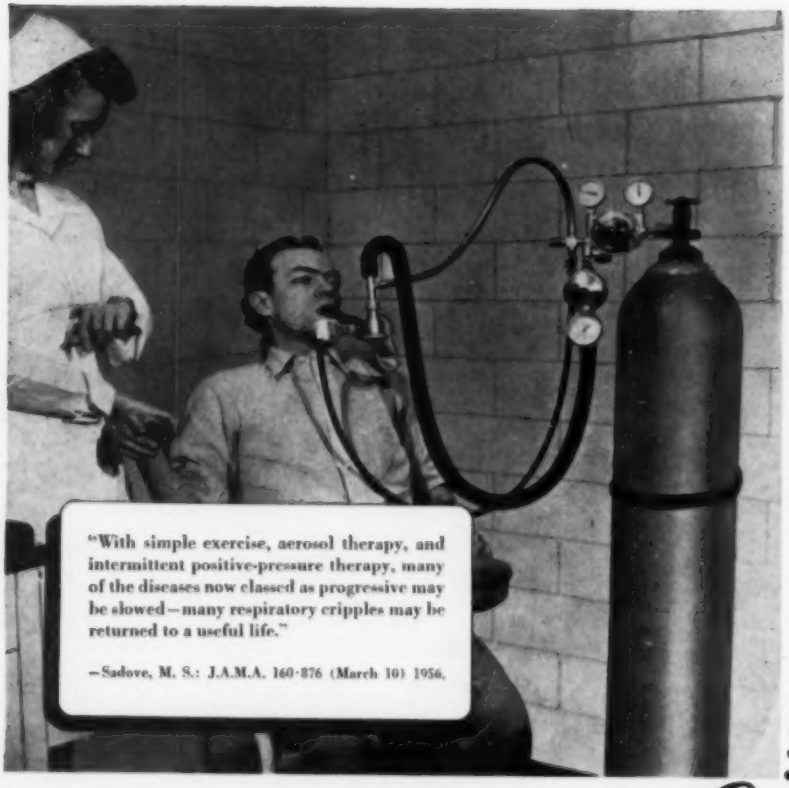
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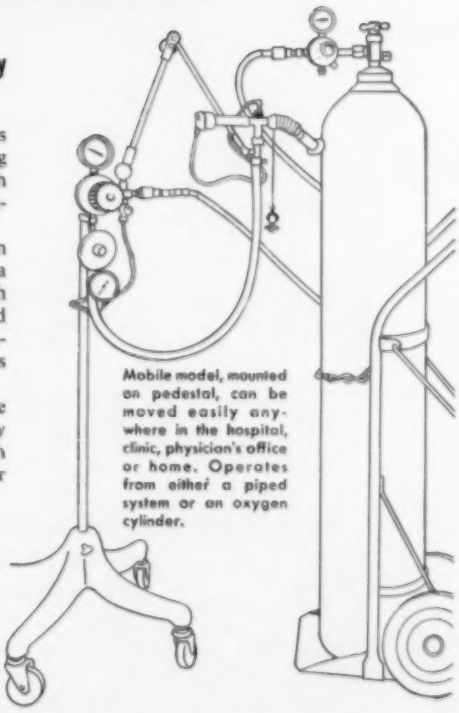

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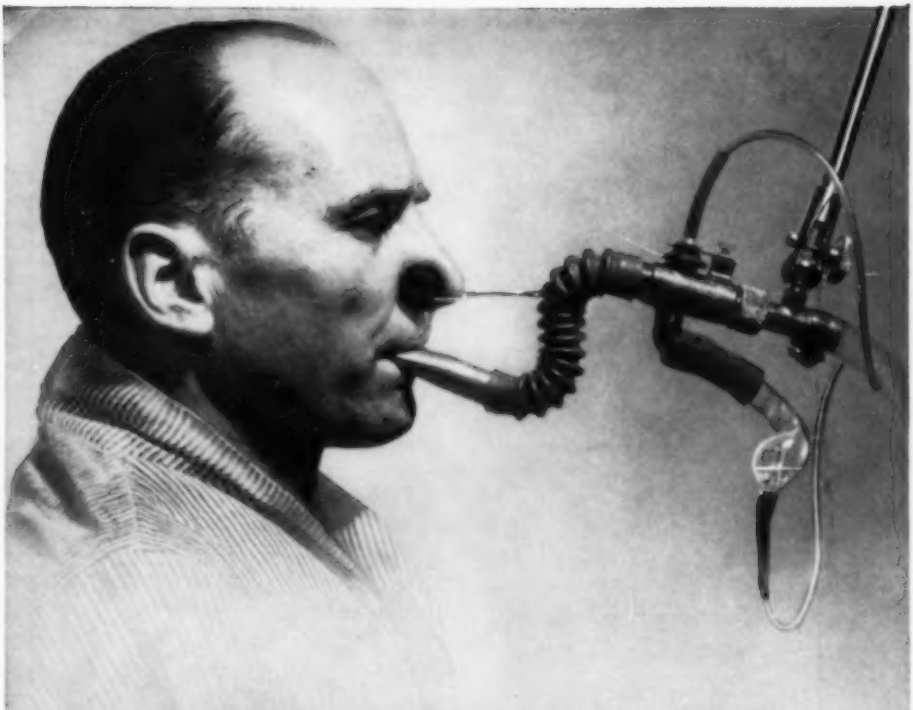

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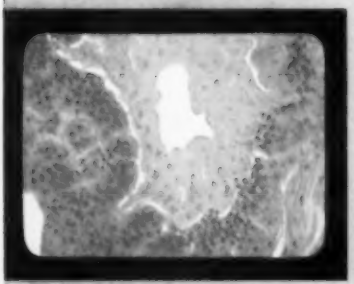

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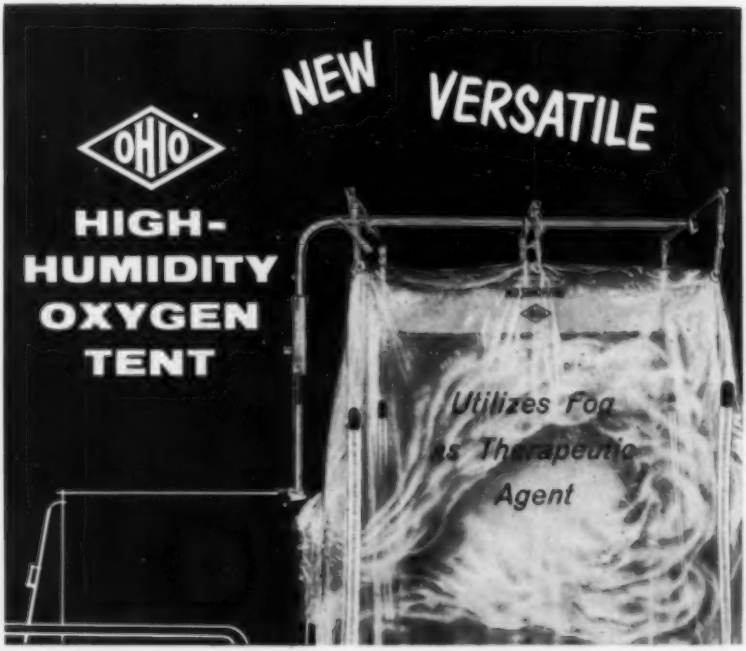

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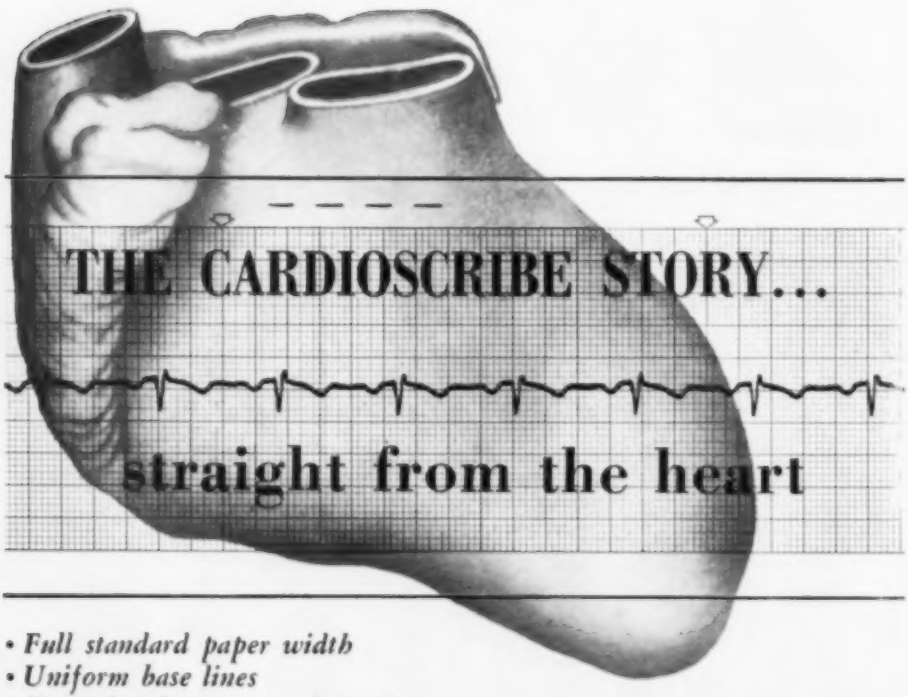

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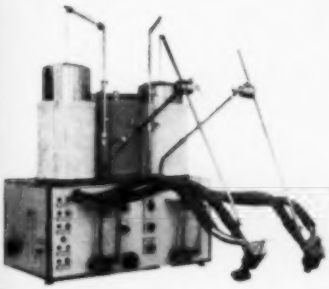

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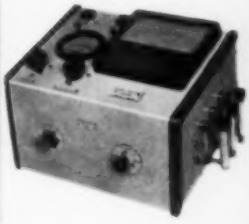

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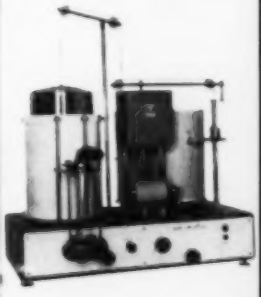

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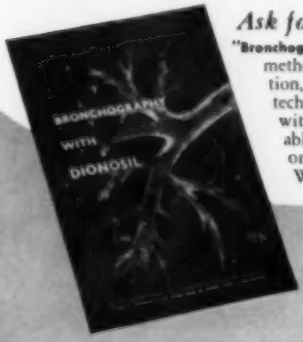

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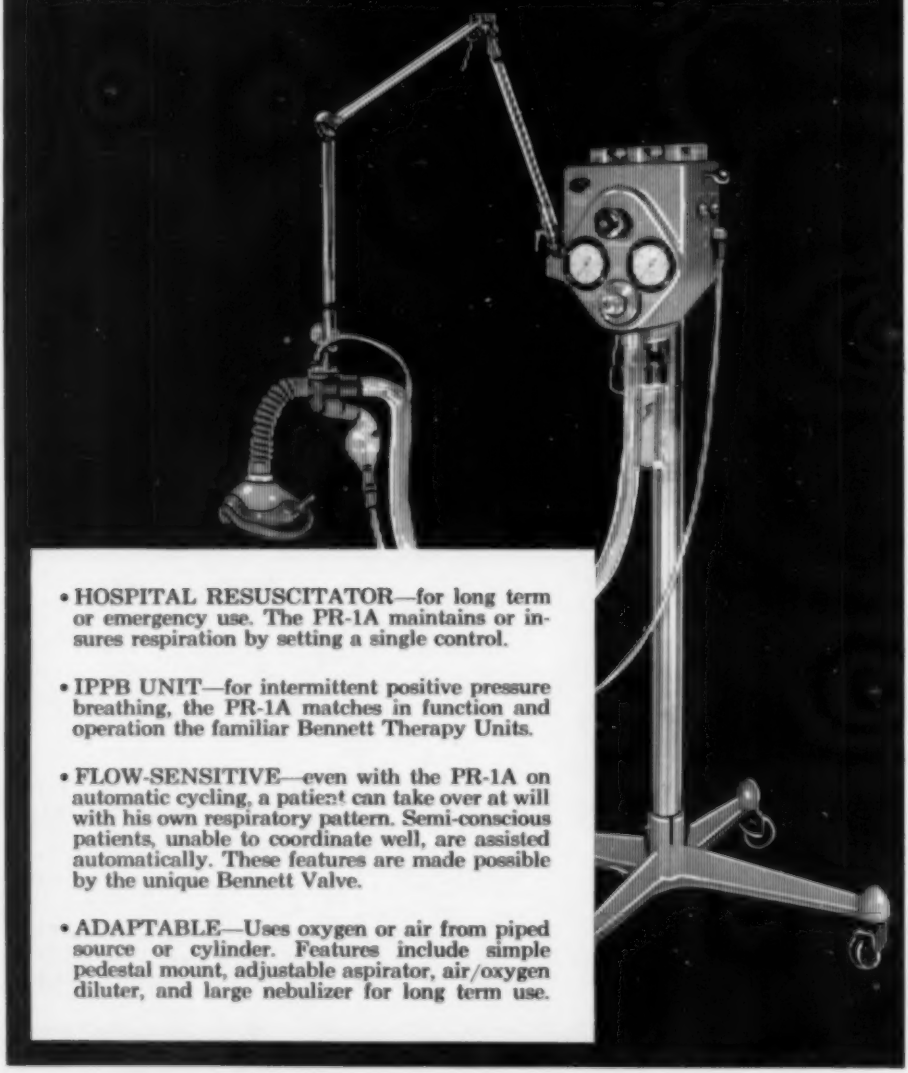

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VOLUME XXXIV OCTOBER, 1958 NUMBER 4

Uncommon Roentgen Patterns of Pulmonary Sarcoidosis*

BENJAMIN FELSON, M.D., F.C.C.P.

Cincinnati, Ohio

The common roentgen features of intrathoracic sarcoidosis have been adequately described and clearly depicted in the literature. Numerous reports illustrate the variegated manifestations of the disease: the lymph node enlargement, the disseminated miliary densities, the localized infiltrates, and the fibrotic changes, alone or in combination.

However, not all cases reveal these more or less typical findings. The present report deals with two interesting but less familiar roentgen patterns of pulmonary sarcoidosis which may, at times, bring this disease to mind—the multinodular and the multicystic.

THE MULTINODULAR PATTERN

This relatively uncommon form of sarcoidosis has received little mention in the literature, only a few cases having been recorded. McCord and Hyman,[1] in 1952, reported and illustrated two cases of pulmonary sarcoidosis in which large parenchymal nodules, indistinguishable from the "snowball" lesions of metastatic malignancy, were demonstrated roentgenographically. Turiaf and Brun,[2] in their monograph on sarcoidosis, reproduced the roentgenograms of another case. There were five large rather well-demarcated nodules, one in the right apex and the others in the lower lung fields. The chest was otherwise normal. Two months later the lesions had almost disappeared. A chest film three years earlier was said to have shown only disseminated miliary densities.

I have had the opportunity of studying the roentgenograms in five cases, including the two reported by McCord and Hyman. In four instances a roentgen diagnosis of malignant pulmonary metastases was originally made. However, the mild clinical symptoms and the continued well-being of the patients led to further study, and ultimately microscopic evidence of sarcoid was obtained, twice from the lung and twice from a peripheral lymph node. In the fifth case, reported below, sarcoid was suspected clinically and roentgenologically and the diagnosis was confirmed by scalene

*From the Department of Radiology, University of Cincinnati College of Medicine, and the Cincinnati General Hospital.

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lymph node biopsy. Four of the five patients were young Negroes and the fifth was a Negress, age 26. All were mildly ill, with general symptoms, such as fever, malaise, night sweats, and weight loss, and respiratory symptoms, such as cough, dyspnea, and expectoration. All but one of the cases showed peripheral lymph node enlargement of slight to moderate degree, and two showed elevation of the serum globulin and serum calcium. No other clinical evidence of systemic sarcoidosis was apparent.

Roentgen Findings. In each case the chest roentgenogram revealed changes far out of proportion to the mild clinical manifestations. There were numerous round or oval lesions, 5 to 40 mm. in diameter, widely distributed in the lungs. In four of the cases the nodules appeared to be more numerous in the central zones, where they tended to be confluent. The individual nodules in these four cases presented a hazy or fluffy outline, the "soft" margin sometimes appearing as a halo around the central density. The confluence of the nodules and their lack of sharp borders did not closely simulate the common type of metastases, but the resemblance to the "halo" nodules of chorionepithelioma, also seen occasionally with other metastatic tumors, was striking. The fifth case showed scattered sharply-outlined nodules varying from about 5 to 15 mm. in diameter, in no way different from the appearance of the garden variety of pulmonary metastases.

In three of the cases the superior mediastinum appeared widened, presumably due to lymph node enlargement. In only one was hilar lymph node enlargement apparent, but in three others the overlying pulmonary lesions obscured the hilar areas.

Follow-up films were obtained in all but the patient with the sharply circumscribed nodules. In one, followed for five months, no change was

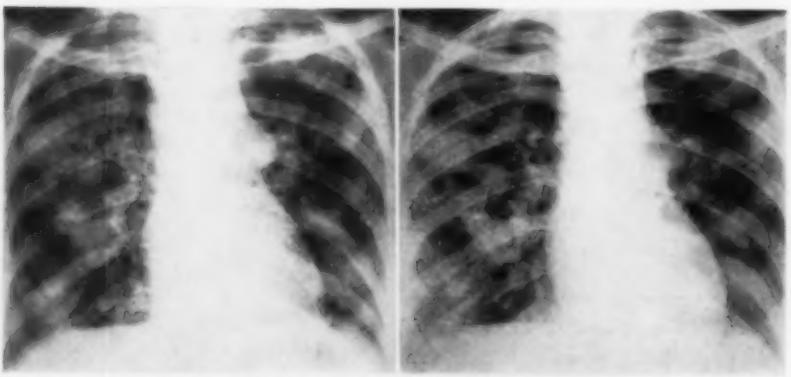

FIGURE 1A FIGURE 1B

Figure 1 (Case 1): Multinodular sarcoidosis. A. August 4, 1957. There are numerous large round and oval coalescent lesions widely distributed in the lungs. The nodules have fluffy margins, giving them a halo-like outline. There is superior mediastinal and left hilar lymph node enlargement. B. August 16, 1957. The nodular densities are distinctly smaller and somewhat less dense.

observed. In another, slight improvement was noted at four months. One case, previously reported,[3] showed a striking change at 10 months, with marked resolution of the large nodules and the superimposition of a fine diffuse miliary pattern. In the following case definite improvement was evident in 12 days and considerable regression was noted at five months.

Case Report

Case 1: (Reported through the courtesy of Drs. I. Leonard Bernstein and Paul F. Fletcher). A. P., a 26 year old colored woman, was first admitted to Jewish Hospital, Cincinnati, in October, 1955, in labor. She delivered a normal full-term infant. A 70 mm. photofluorographic chest film appeared normal. In May, 1956, another routine photofluorographic chest film was normal.

On August 3, 1957, she was re-admitted because of a dry non-productive cough, intermittent fever, night sweats, and a weight loss of five pounds. The cough had been present for five months, but the other symptoms were of more recent origin. She was not acutely ill, and had no fever on admission. Physical examination was normal except for fine rales and inspiratory wheezes at the lung bases.

Blood counts and smear were normal except for an eosinophilia of 9 per cent, which soon fell to normal. The sedimentation rate was 34 mm. No sputum was expectorated. The serum albumin, globulin, and calcium levels were normal, as were all other laboratory studies. Skin tests with tuberculin (second strength) and histoplasmin were negative. Biopsy of a scalene lymph node revealed the histological picture of sarcoid. Pulmonary function studies were interpreted as indicating a restrictive process, compatible with the clinical diagnosis of sarcoidosis.

The chest roentgenogram on August 4 (Fig. 1A) revealed numerous large round and oval coalescent lesions, 1 to 4 cm. in diameter, widely distributed throughout both lungs. The margins of the nodules were ill-defined and fluffy. There was widening of the superior mediastinum and a nodular prominence in the left hilum thought to represent enlarged lymph nodes. On August 16 the chest film showed moderate improvement, many of the nodules appearing distinctly smaller (Fig. 1B).

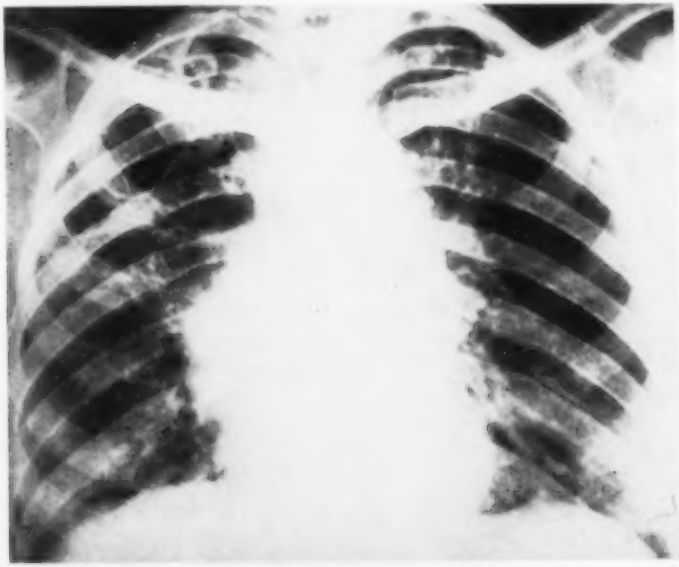

FIGURE 2: There are large and small bullae in the right apex and small ones in the left. The hila and superior mediastinum are widened and somewhat lobulated in outline.

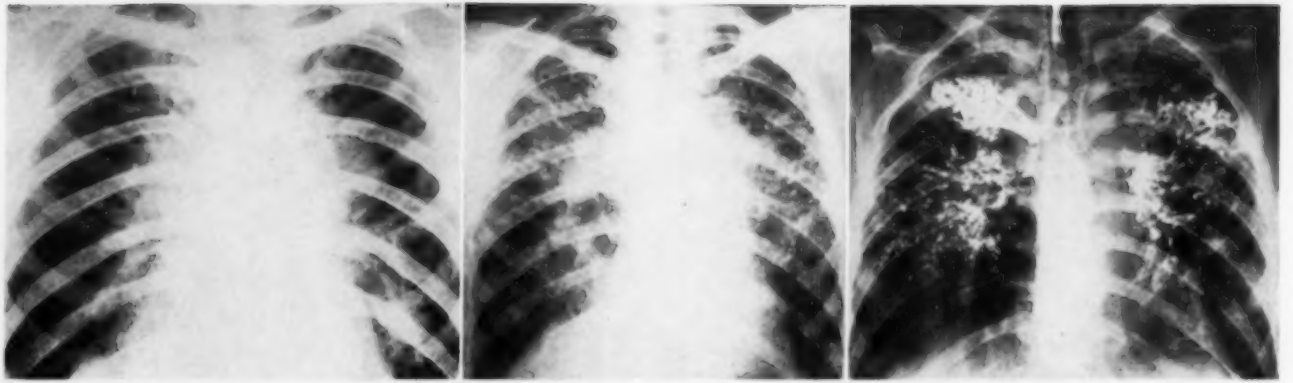

FIGURE 3A FIGURE 3B FIGURE 3C

Figure 3: (Courtesy of Dr. Lee S. Rosenberg). A. January, 1944. Diffuse miliary nodulation; marked tracheobronchial lymph node enlargement. B. December, 1952. Innumerable small round radiolucencies are now present in the upper two-thirds of both lungs. The lymph node enlargement is still quite striking. Residual lipiodol is present in the lungs. C. Bronchogram. There is extensive cystic bronchiectasis. In the upper lobes the bronchi are crowded together.

She improved promptly on steroids and was discharged, symptom-free, on August 19, 1957. She has remained clinically well since that time. Chest roentgenograms in March, 1958, showed about 75 per cent regression in the size of the pulmonary nodules and the hilar and mediastinal enlargement had almost completely disappeared.

Comment

The multinodular roentgen pattern described above cannot, of course, be considered diagnostic of sarcoidosis. It is a rare manifestation of this disease and perhaps would more often result from tumor metastases or pulmonary lymphoma. Multiple histoplasmomas, the nodular form of tuberculosis, and multiple benign tumors (e.g. hamartomas) must also be considered in differential diagnosis, but in these conditions the nodules are fewer in number and sharper in outline, and often some of them contain calcium.[3]

Certain features encountered in the present group of cases should provide the clue to the correct diagnosis. These include the mild clinical symptoms and the continued well-being of the patients; the presence in other body systems of stigmata consistent with sarcoidosis, especially lymphadenopathy; the apparent predilection for young Negroes; the fluffy margins of the pulmonary nodules and their tendency to become confluent; and the stationary or even regressive course shown roentgenographically.

THE MULTICYSTIC PATTERN

The multicystic pattern of sarcoidosis is probably a complication of the irreversible fibrotic stage of the disease. It is not infrequently encountered at the autopsy table in patients dying of sarcoidosis but has seldom been emphasized as a prominent or predominant roentgen manifestation of the disease. Individual cases have been reported and occasional examples have been included in articles dealing with the roentgen manifestations of sarcoid,[4-16] but few authors have dwelt on this phase of the disease.

Longcope and Freiman,[6] in their classical monograph on sarcoidosis, stated that the large cavitary lesions seen on roentgenograms usually proved to be emphysematous bullae or cystic bronchiectatic dilatations. They pointed out that the emphysema resulted from extensive diffuse pulmonary fibrosis, and that when such changes were demonstrable complete regression was no longer possible.

In their monograph on intrathoracic sarcoidosis, Turiaf and Brun[2] devoted considerable discussion to this subject and illustrated local and widespread forms of bullous emphysema as well as a reversible type. They noted a good correlation between the extent of the emphysema and the severity of the symptoms and signs, and recorded such complications as pneumothorax, fluid levels from secondary infection, and cor pulmonale.

Mallory[11] reported the autopsy findings of six patients who died of extensive long-standing pulmonary fibrosis. He noted widespread coarse emphysema, with bullae ranging up to a centimeter in diameter in all the cases. Microscopically, numerous non-caseating miliary tubercles were also present. He considered it probable that these cases were examples of sarcoidosis.

FIG. 4A

FIG. 4B

FIG. 4C

Figure 4 (Case 2): A. January, 1954. Infiltrate is present in both upper lobes and both hila are elevated. The right hilum is enlarged. B. November, 1956. Moderately large bullae (arrows) have replaced much of the infiltrate. The trachea is deviated to the right. Bilateral hila rand mediastinal enlargement is present. C. Lordotic view shows the emphysematous bullae and lymph node enlargement to better advantage.

Our experience with the multicystic pattern of sarcoidosis dates back about 10 years and is based on nine proved cases. Six were seen at the Cincinnati General Hospital and represent 21 per cent of the 28 proved cases of sarcoid at this institution in which chest roentgenograms were available. The remaining three cases came from other institutions in the Cincinnati area.

All six cases from the General Hospital were Negro (Negroes account for about 50 per cent of the hospital admissions) but the three outside cases were white. There were five women and four men in the group. The ages ranged from 29 to 63 years, with an average of 38 years. Comparable figures for the control group of 22 cases of sarcoid from the General Hospital who did not show the multicystic pattern were as follows: 22 Negro, 0 white; 18 women, 4 men; age range 19 to 49 with an average of 31 years, seven years less than that of the multicystic group.

Of the nine multicystic cases, eight had chronic cough and five had hemoptysis. Dyspnea and expectoration were prominent symptoms, but weight loss was infrequent. Two had recurrent episodes of acute pneumonia. Only one, a patient with relatively minimal pulmonary changes, was asymptomatic. Evidence of cor pulmonale was present in three of the multicystic and in none of the control cases. The incidence of involvement of the skin, peripheral lymph nodes, liver, spleen, eyes, salivary glands, and bones in the cystic cases was approximately the same as in the control group. Renal calculi were encountered once in each group, and abnormal levels of serum calcium and serum proteins also occurred with equal frequency in the two groups.

Five of the nine multicystic cases died, and autopsy was performed in three. In each, widespread pulmonary and pleural fibrosis were found, associated with bullous emphysema and bronchiectasis. In two, miliary granulomas consistent with sarcoid were found microscopically in the lung and other viscera. In the third, no evidence of sarcoid was demonstrated at autopsy, although several years earlier the diagnosis had been established by clinical, roentgen, and histologic findings.

Roentgen Findings. On the initial roentgenogram multicystic lesions were the predominant feature in only one case, although they were present to some degree in several others. In the remaining eight, extensive pulmonary infiltrate was apparent, fibrotic in nature in six and miliary in two. In two cases, one with fibrosis and one with miliary densities, the involvement was limited to one lung. The unilateral miliary lesions exemplified an exceedingly rare distribution of this form of sarcoidosis. Mediastinal and/or hilar enlargement was evident on the first film in seven cases and appeared later in one. Spontaneous pneumothorax occurred terminally in one case.

Two cases were followed roentgenologically for less than six months. In the other seven, chest films were available for a period of from three to nine years. In these, once the cystic lesions appeared, they increased slowly in number and extent. In no instance did regression occur; instead, there was gradual progression with partial transformation of the fibrotic

process into cystic lesions. In one of the two cases presenting a miliary pattern, this was subsequently replaced by fibrosis before the bullae developed.

The ultimate appearance was often quite characteristic (Figs. 2, 3, and 4). There was widespread involvement of the lungs with strand-like or ill-defined densities honeycombed with large or small thin-walled cavities having the typical appearance of bullae in seven cases and of cystic bronchiectasis in two. In addition—and an important part of the picture—there was definite enlargement of the hila and/or the superior mediastinum. The margins of the broadened mediastinum lacked the usual sharp definition seen in the earlier stages of sarcoidosis because the adjacent pulmonary lesions overlapped and obscured them to some degree.

In two cases bronchograms were obtained late in the course of the disease. Both revealed moderately extensive cystic bronchiectasis; in addition, one showed crowding of the bronchi in the upper lobes, indicating collapse or fibrosis (Fig. 3).

In the differential diagnosis any condition which causes widespead pulmonary fibrosis which, in turn, results in bullous emphysema or cystic bronchiectasis, must receive consideration. Many diseases fall into this category,[17] including tuberculosis, histoplasmosis, diffuse interstitial fibrosis of Hamman and Rich, scleroderma, bronchiectasis, progressive bullous emphysema or "vanishing lung," pneumoconiosis, and the later stages of chronic bronchial asthma. These conditions often closely simulate multicystic sarcoidosis roentgenologically as well as clinically. However, the enlarged tracheobronchial nodes, earlier chest roentgenograms showing the more typical appearance of sarcoid, and the presence of other clinical and laboratory evidence consistent with sarcoidosis suggested the correct diagnosis in a number of the cases in the present series.

Case 2: S. O., a 31 year old colored woman, was admitted to Cincinnati General Hospital October 29, 1956, with a history of dyspnea, cough, and expectoration associated with bouts of fever. Past history revealed that she had been a patient in a tuberculosis sanatorium rather briefly in 1954 and again in 1957 with similar complaints. A diagnosis of pulmonary tuberculosis had been made but sputums were repeatedly negative. On the present admission physical examination revealed moderate respiratory distress, evidence of weight loss, bilateral inspiratory rales over the apices, and dullness and decreased fremitus over the right lung.

A chest film (Fig. 4B) showed infiltrate in both upper lobes, in which thin-walled radiolucencies having the appearance of bullae were apparent. The hilar shadows were elevated and enlarged and the superior mediastinum was slightly widened. The cardiac contours were obliterated by adjacent pulmonary involvement. A roentgen impression of tuberculosis or sarcoidosis was made. The 1954 films from the sanatorium were obtained (Fig. 4A) and revealed the infiltrate in both upper lobes and right hilar enlargement. Bullae were not evident.

Multiple sputum examinations were negative for tubercle bacilli and fungi. The electrocardiogram revealed right ventricular hypertrophy. The serum calcium and the serum albumin and globulin were normal. There was considerable respiratory impairment shown by pulmonary function studies. Biopsy of a scalene node showed miliary non-caseating granulomas, consistent with sarcoid. She was discharged December 8, somewhat improved symptomatically. She was readmitted on December 23 for cardiac catheterization. Following this procedure she became nauseated and apprehensive, and complained of right chest and shoulder pain. Her blood pressure fell, she responded poorly to emergency care, and died two days later.

Autopsy revealed large conglomerations of lymph nodes in the mediastinum. Pleural effusions were present bilaterally but the pleural surfaces appeared normal. The right

lung weighed 500 grams and the left 360. Numerous bullae were seen throughout the lungs. On cut section the lung parenchyma appeared markedly fibrotic and honeycombed. The bronchioli were quite prominent. The right ventricle was dilated and its wall thickened. There was thrombosis of the right atrial appendage. No other significant finding was noted.

Microscopically, the lungs showed distortion of the parenchyma with marked interstitial pneumonitis of nonspecific nature and striking fibrosis of the alveolar septa. In the walls of the small and large bronchi there was much scarring, and many giant cells containing large Schaumann bodies were seen. Scattered non-caseating granulomas were present in the lungs, lymph nodes, heart, spleen, and liver. Final diagnoses were sarcoidosis, pulmonary fibrosis, bullous emphysema, bronchiectasis, cor pulmonale, and thrombosis of the right atrial appendage.

Comment

The seriousness of the multicystic form of pulmonary sarcoidosis is evident when it is pointed out that five of the nine cases have died and that two others were doing poorly when last seen. One did well but was followed for only a month. The other had moderate symptoms five years after bullae first became evident. The causes of death in the five cases were respiratory insufficiency and/or cor pulmonale in four, and tension pneumothorax in one.

The sequential roentgenograms appear to substantiate the viewpoint that the cystic changes result from pulmonary fibrosis. While it is realized that the roentgen recognition of fibrosis is not always reliable, the criteria used in the present cases seem adequate. These included strand-like densities, persistence of the shadows for periods in excess of a year, and retraction of fissures, hila, and mediastinal structures.

It is, of course, realized that there is no microscopic picture which is pathognomonic for the diagnosis of sarcoid.[11] However, the presence of compatible clinical and roentgen findings, when added to the demonstration of non-caseating granulomas, leaves little doubt that these patients suffered from sarcoidosis. It is also apparent that the multicystic pattern represents a late manifestation of this disease.

SUMMARY

The present report deals with two interesting but less familiar roentgen patterns of pulmonary sarcoidosis, the multinodular and multicystic. The former consists of multiple large nodules simulating those of malignant pulmonary metastases. The multicystic type is probably a complication of the fibrotic stage of sarcoidosis, the cysts representing emphysematous bullae and bronchiectatic cavities. The clinical and roentgen features encountered in a group of five cases presenting the multinodular and nine cases showing the multicystic pattern are described and their importance in differential diagnosis emphasized. Criteria are set forth which should suggest the diagnosis of sarcoidosis in such cases.

Acknowledgments: The author wishes to thank Drs. Helen Ackerman, I. Leonard Bernstein, Paul F. Fletcher, Hans Plaut, and Lee S. Rosenberg for permission to include their cases, and to Drs. Rosenberg and David G. Freiman for reviewing the manuscript.

RESUMEN

Esta comunicación se refiere a dos aspectos radiológicos interesantes pero menos comunes de la sarcoidosis pulmonar, la forma multinodular y poliquística. La primera consiste en grandes nódulos numerosos que simulan los de las metástasis pulmonares. La forma poliquística en una complicación probable de la etapa fibrosa de la sarcoidosis, siendo los quistes bulas enfisematosas y cavidades bronquiectásicas. Las características clínicas y radiológicas encontradas en este grupo de cinco casos que presentan el aspecto multinodular y nueve casos de forma poliquística se describen de acuerdo con su importancia y se recalca el diagnóstico diferencial.

Se establecen criterios que sugerirían el diagnóstico de sarcoidosis en tales casos.

RESUME

La présente communication se rapporte à deux images radiologiques de sarcoïdose pulmonaire intéressantes, mais peu communes; l'aspect multinodulaire et multikystique. Le premier consiste en nodules multiples étendus, simulant ceux des métastases pulmonaires malignes. La forme multikystique est probablement une complication de l'état fibreux de la sarcoïdose, les kystes représentant des bulles emphysémateuses et des cavités bronchiectasiques. L'auteur décrit les caractères cliniques et radiologiques rencontrés dans un groupe de cinq cas présentant la forme multinodulaire, et neuf cas montrant un aspect multikystique, et il met en lumière leur importance dans le diagnostic différentiel. Il propose des critères qui permettraient d'évoquer le diagnostic de sarcoïdose dans de tels cas.

ZUSAMMENFASSUNG

Die vorliegende Mitteilung berichtet über 2 interessante, jedoch weniger bekannte röntgenologische Erscheinungsformen der pulmonalen Sarkoidose, nämlich die multinoduläre und die multizystische Form. Die erstgenannte besteht aus multiplen grossen Knoten, die maligne pulmonale Metastasen vortäuschen. Der multizystische Typ ist wahrscheinlich eine Komplikation des fibrotischen Stadiums der Sarkoidose, wobei die Zysten Emphysembläschen und bronchiektatische Kavernen darstellen. Es werden die klinischen und röntgenologischen Eigenschaften beschrieben, die in je einer Gruppe von 5 Fällen des multinodulären und 9 des multizystischen Typs angetroffen werden, und ihre Bedeutung in differentialdiagnostischer Hinsicht wird hervorgehoben. Es werden Kriterien aufgezeigt, die die Diagnose eines Sarkoids in solchen Fällen nahe legen.

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A Characterization of Atypical Acid-Fast Bacilli Obtained from Patients with Pulmonary Tuberculosis*, **

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Introduction

The increasing use of simple and effective cultural techniques for the isolation of tubercle bacilli has been most valuable in confirming the diagnosis of tuberculosis and evaluating the activity of the disease in any given patient. However, as a by-product of this increasing reliance upon the cultural isolation of tubercle bacilli from sputum, gastric contents, or other secretions, more frequent reports are appearing concerning the isolation of atypical acid-fast bacilli from such sources.[1-10] In many instances it is difficult to assess the etiologic relationship of such atypical organisms to the disease encountered in the patient from which they originated.[1-11] However, it is essential that these organisms are properly characterized so that diagnosis can be made and, when indicated, chemotherapy can be initiated or continued.

Upon reviewing 649 culture-positive, consecutive cases, studied diagnostically in our laboratory from February, 1955, to November, 1956, we found that 164 patients had cultures reported positive for atypical acid-fast bacilli at one time or another. This was an incidence of slightly more than 25 per cent. The atypical cultures obtained in this series had been stored and they formed the basis of this report which details the results of our efforts to characterize these organisms and to relate the findings to the clinical disease found in the patients.

Materials and Methods

The ultimate basis for judging a culture to be atypical was made upon a careful inspection of colonial morphology. It was immediately apparent that the 164 atypical strains isolated from our patients fell in three groups which generally conformed to those described by the "Cooperative Study of Mycobacteria."[12] For purposes of clarity the three groups may be differentiated as follows:

Group I: Photochromogenic strains. These form a lemon yellow pigment during growth if exposed to light. This group comprised 22.6 per cent of our atypical cultures isolated from patients.

This investigation was supported (in part) by Research Grant E 1174 from The National Institute of Allergy and Infectious Diseases, Public Health Service.

Suburban Cook County Tuberculosis Sanitarium District, Hospital-Sanitarium.

*Presented in part before the Sixteenth Veterans Administration-Armed Forces Conference on The Chemotherapy of Tuberculosis, St. Louis, Missouri, February 12, 1957.

**Presented before the Medical Session as part of Section 2B at the Annual Meeting of the National Tuberculosis Association, Kansas City, Missouri, May 7, 1957.

TABLE IA

SUMMARY OF DATA OBTAINED FROM TYPICAL AND ATYPICAL CULTURES

		Cellular Morphology			Reduction of Dyes[3]				
A. Typical Cultures	Medium of Primary Isolation[1]	Cording[2]	Average Bacillary Length in Micra	Granules	Sodium Dibromoindophenol	Indophenol	Neutral Red Test	Catalase Reaction	Clinical Status
1 (L. Z.)	B.	+	3.0	0	0	0	+	+	Min.
3 (E. M.)	B.	+	3.0	0	0	0	+	+	Min.
5 (E. J.)	L.	+	2.0	0	0	0	+	+	Mod. Adv.
10 (I. C.)	B.	+	2.5	0	0	0	+	±	Min.
11 (H. H.)	A. A.	+	3.0	0	0	0	+	+	Far Adv.
15 (C. P.)	B.	+	2.5	0	0	0	+	+	Far Adv.
21 (P. G.)	L.	+	3.0	0	0	0	+	±	Far Adv.
22 (R. R.)	B.	+	3.0	0	+	+	+	+	Far Adv.
26 (I. R.)	L.	+	3.5	+	0	0	+	+	Far Adv.
28 (R. R.)	B.	+	3.5	+	0	0	+	+	Far Adv.
32 (E. L.)	A. A.	+	3.0	+	0	0	+	+	Far Adv.
B. Group I Cultures									
6 (H. S.)	L.	0	2.0	+	+	+	—	++	Far Adv.
7 (E. M.)	B.	±	2.0	+	0	0	—	++	Min.
9 (E. K.)	L.	0	3.0	+	+	+	—	++	Far Adv.
13 (F. T.)	A. A.	+	2.0	+	++	++	—	++	Mod. Adv.
14 (E. E.)	L.	0	2.0	+	++	+	—	++	Far Adv.
17 (R. C.)	L.	±	2.5	0	++	++	—	++	Mod. Adv.
24 (H. N.)	L.	±	1.5	+	++	++	—	++	Far Adv.
27 (S. H.)	B.	±	10.0	+	++	++	—	++	Mod. Adv.
29 (W. N.)	A. A.	±	2.5	+	++	++	—	++	Far Adv.
30 (R. B.)	L.	+	3.0	+	0	++	—	++	Far Adv.
34 (D. K.)	A. A.	0	3.0	+	++	+	—	++	Min.
36 (G. S.)	B.	+	2.5	+	++	++	—	++	Min.

[1] B = Tarshis Blood Medium; L = Lowenstein Medium; A. A. = Modified Dubos Albumin Agar Medium.

[2] + = Definite Cording; ± = Partial Cording; 0 = No Cording.

[3] 0 = No Reduction; + = Partial Reduction; ++ = Complete Reduction.

Group II: Non-photochromic strains. These are white, beige, or buff to yellowish; the pigmentation, if any, is not light conditioned. This group comprised 2.4 per cent of the atypical cultures isolated.

Group III: Deeply chromogenic yellow-orange strains which are pigmented even in complete darkness (skotochromogenic). This group comprised 75 per cent of the atypical cultures isolated.

Twenty-five cultures of atypical acid-fast bacilli were selected for detailed study and they included 12 strains of Group I, three of Group II, and 10 of Group III. They were compared in all respects with 11 cultures of typical human type tubercle bacilli. All cultures which were used for this study were isolated from one of the following diagnostic media routinely used in this laboratory: (1) Lowenstein (Jensen Holm Modification);[13] (2) Blood Medium;[14] and (3) Modified Dubos Albumin Agar Medium.[15]* The specific characteristics which we studied consisted of the following: (1) Colonial morphology; (2) Cellular morphology; (3) Rate of growth in liquid medium; (4) Oxidation-Reduction of dyes; (5) Neutral red test; (6) Catalase reaction; (7) Drug sensitivity; (8) Guinea pig virulence; (9) Clinical course in humans; and (10) Correlation between histopathology and bacteriology of resected specimens whenever available.

Initially, a loopful of each culture, obtained from growth on solid medium, was transferred into a tube containing 5 ml. of Dubos Tween 80 liquid medium[16] and triturated. These liquid cultures were incubated at 37° C. for seven days and all sub-cultures were made subsequently from them. All cultures were coded by numbers which were assigned blindly and their source was not divulged until the tests were completed.

1. *Colonial Morphology*

Growth on Lowenstein medium was used for the analysis of colony character and pigmentation. For this purpose, inocula consisting of single loopfuls of seven day liquid Dubos cultures were placed on individual Lowenstein plates and these were incubated for 21 days in the dark and

Footnote:

*Basal Medium[15]

$K H_2 PO_4$	1.0 gm.
$Na_2 H PO_4 o 12 H_2O$	6.3 gm.
Asparagine	2.0 gm.
Dist. water	100.00 ml.

Heat to dissolve and add

Dist. water	750 ml.
Casein digest	2.0 gm.
Fe NH_4 Citrate	0.05 gm.
Mg $SO_4 o 3 H_2O$	0.006 gm.
Ca Cl_2	0.0005 gm.
Zn SO_4	0.0001 gm.
Cu SO_4	0.0001 gm.

Adjust pH to 6.5-6.8 and add

Agar 20.0 gm.
Green vegetable coloring 0.1 ml.
Autoclave 15 minutes at 20#.
Add aseptically to Agar base cooled to 50° C.

Bovine Albumin Fraction V—10 gm.
(200 ml. of 5% solution of albumin in 2% saline, neutralized, inactivated at 56° C. for ½ hour and sterilized by filtration through a Seitz filter.)
Glucose—10 gm.
(20 ml. of an autoclaved 50% solution)
Penicillin—5000 units in sterile distilled water
Tube aseptically.

then inspected. All cultures were left in the light at room temperature for 24 hours and then re-examined for the acquisition of or changes in pigment. Colonial morphology was noted in every instance.

2. *Cellular Morphology*

Sub-cultures of each strain in Dubos Tween 80 medium were prepared and their growth was carefully observed photelometrically. When maximum rate of growth was obtained, smears were made and stained with modified Kinyoun Stain.[17]* The stained smears were carefully examined and the appearance of the individual cells characterized and their size measured. The presence or absence of granules and tendency to cord were noted.

TABLE 1B

SUMMARY OF DATA OBTAINED FROM TYPICAL AND ATYPICAL CULTURES

		Cellular Morphology			Reduction of Dyes[3]				
C. Group II Cultures	Medium of Primary Isolation[1]	Cording[2]	Average Bacillary Length in Micra	Granules	Sodium Dibromoindophenol	Indophenol	Neutral Red Test	Catalase Reaction	Clinical Status
2 (T. H.)	B.	0	2.0	0	+	+	—	+	Far Adv.
4 (S. M.)	B.	±	2.0	0	+	++	—	++	Far Adv.
18 (E. M.)	A. A.	±	3.5	0	+	0	—	++	Mod. Adv.
D. Group III									
8 (F. K.)	B.	0	1.5	+	++	+	+	++	Far Adv.
12 (S. Z.)	B.	0	1.5	+	++	++	—	++	Mod. Adv.
14 (G. O.)	B.	0	2.0	+	+	+	—	++	Mod. Adv.
16 (J.K.)	A. A.	0	1.5	+	+	++	+	++	Far Adv.
20 (J. K.)	L.	0	2.0	+	+	+	+	++	Far Adv.
23 (R. S.)	L.	0	2.0	+	++	++	—	++	Far Adv.
25 (I. R.)	L.	±	1.5	+	++	++	—	+	Far Adv.
31 (D. C.)	L.	±	1.5	+	+	+	—	++	Min.
33 (R. Y.)	L.	0	3.0	+	++	+	—	++	Min.
35 (G. B.)	L.	0	1.5	+	+	0	—	++	? Tbc.

[1] B = Harshis Blood Medium; L = Lowenstein Medium; A. A. = Modified Dubos Albumin Agar Medium.

[2] + = Definite Cording; ± = Partial Cording; 0 = No Cording.

[3] 0 = No Reduction; + = Partial Reduction; ++ = Complete Reduction.

*The original Kinyoun carbolfuchsin stain was used in conjunction with the Ziehl-Neelsen decolorizer and methylene blue counterstain.

3. *Rate of Growth*

The following simple technique was devised as a means of characterizing the various cultures studied in terms of their rate of growth and duration of initial lag phase. A 0.1 ml. volume from the initial seven day liquid culture of each strain was inoculated into 7.5 ml. of Dubos Tween 80 medium in individual Klett tubes which were then incubated at 37° C. Utilizing a Klett-Summerson photocolorimeter, Model 800.3, daily readings were made and recorded on each culture.

4. *Oxidation-Reduction of Dyes and Neutral Red Test*

After the determination of gross colony morphology, the 21 day cultures on Lowenstein medium were used as the source material for oxidation-reduction dye and neutral red tests. The dyes selected for the oxidation-reduction tests were indophenol sodium and 2, 6 dibromoindophenol sodium and the technique utilized was that described by Wilson, et al.[18] as modified by Wrinkle and Patnode.[19] The neutral red tests were done according to the procedure described by Dubos and Middlebrook.[20] Cultures of M. phlei, M. butyricum, M. smegmatis and M. ranae were included in the series of both tests in order to evaluate their specificity.*

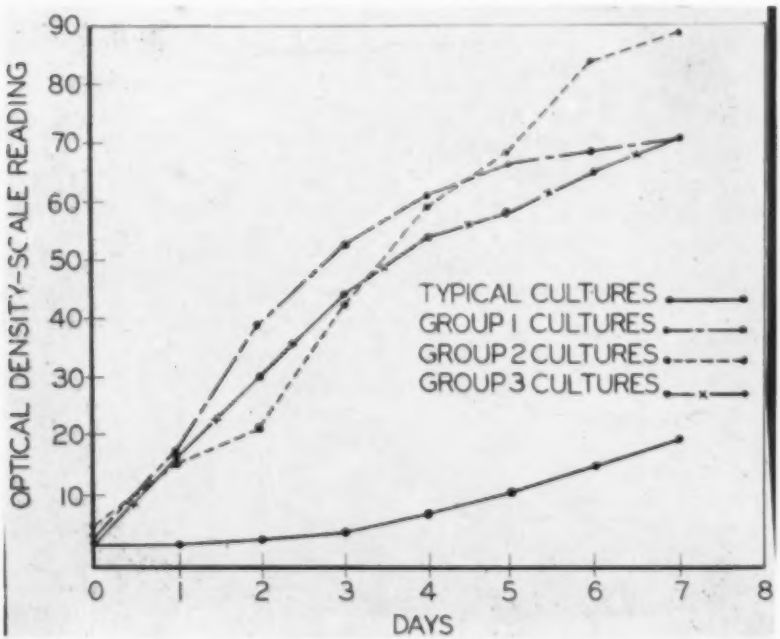

FIGURE 1: Growth of typical and atypical acid-fast cultures in liquid Dubos-Tween 80 medium.

*Kindly provided for this study by Dr. Guy Youmans, Department of Bacteriology, Northwestern University Medical School.

5. *Determination of Catalase Activity*

Actively growing cultures on Lowenstein medium were employed for the catalase test according to the procedure outlined by Middlebrook.[21] A drop of the peroxide-tween solution at room temperature was deposited upon the culture to be tested. The active evolution of gas bubbles within two or three seconds was interpreted as a highly positive (++) catalase reaction. If there was marked gas formation within seconds, the test was reported moderately positive (+). The production of slight but definite amounts of gas within a thirty second period was interpreted as a weakly positive (±) catalase reaction.

6. *Drug Sensitivity*

The sensitivity or resistance of each culture to the standard anti-tuberculous drugs was determined by the following method. A volume of 0.1 ml. of the initial seven day liquid culture was placed in quadrants of Felsen plates containing standard Lowenstein medium and varying drug concentrations as follows: isoniazid, 0.2, 1.0, and 5 mcg. per ml.; streptomycin, 3.0, 10 and 100 mcg. per ml.; and PAS 0.1, 1.0, and 10 mcg. per ml. In the preparation of the medium a 50 per cent loss of isoniazid and PAS in the medium was assumed to occur and the concentrations of these drugs were adjusted to compensate for this. However, no drug loss was anticipated to occur in the case of streptomycin. The results of the drug sensitivity tests were determined after 14 days incubation at 37° C. It should be pointed out that the typical cultures were initially selected so that their drug sensitivities would approximate more closely the levels encountered in the atypical strains. In order to accomplish this the typical cultures were obtained from patients who had been on long-term chemotherapy and they were not selected from primary isolations.

7. *Guinea Pig Virulence*

Subcultures of each strain in Dubos Tween 80 medium were prepared. These were observed photelometrically and at the time they were in the

TABLE II

RESULTS OF OXIDATION-REDUCTION DYE TESTS ON TYPICAL, ATYPICAL AND SAPROPHYTIC ACID-FAST CULTURES

	Dibromoindiphenol Sodium			Indophenol		
	Complete Reduction	Partial Reduction	No Reduction	Complete Reduction	Partial Reduction	No Reduction
Typical Cultures	0	1	10	0	1	10
Group I Cultures	8	2	2	7	4	1
Group II Cultures	0	3	0	1	1	1
Group III Cultures	5	5	0	5	4	1
Saprophytic Cultures	4	0	0	4	0	0

maximum growth phase (7-15 days) were transferred to Hopkins vaccine tubes and centrifuged at 3,000 r.p.m. for 30 minutes. One cubic mm. of sedimented cells was assumed to equal one mg. wet weight of tubercle bacilli.[22] Two tuberculin negative guinea pigs were inoculated, one subcutaneously and one intraperitoneally, with each strain. One cubic mm. of sedimented cells, suspended in 0.5 ml. of sterile, distilled water was used for each guinea pig inoculation. The animals were weighed and tuberculin tested (O.T. 1:30) weekly. The guinea pigs which died were autopsied, gross pathology was noted, direct smears for acid-fast bacilli were made of the organs involved, and cultures were made of the spleens. At six weeks the surviving guinea pigs were sacrificed and examined in the same manner as those which had died.

8. *Clinical Course and Correlation with Resected Specimens*

The clinical course of each patient included in this study and the role of the atypical bacilli as etiologic agents were carefully evaluated. When available, surgical specimens were cultured and the character of the gross and microscopic pathology determined.

Results

Since the validity of the initial tentative classification of the atypical cultures into three groups was immediately strengthened and confirmed, the specific results obtained in this study will be discussed within these categories. The basic information obtained is summarized in Table I, which also specifies the origin of both the typical and atypical acid-fast cultures included in the series.

An evaluation of the appearance and pigmentation of the colonial growth on Lowenstein medium before and after exposure to the light was most meaningful. The results obtained were found to be consistent within themselves and to have significance in terms of all of the other factors tested.

1. *Colonial Morphology*

a. Typical—Growth originating from these cultures developed cream-colored, discrete colonies which showed no change in color as a consequence of 24 hours exposure to light at room temperature.

TABLE III

RESULTS OF NEUTRAL RED TESTS ON TYPICAL, ATYPICAL AND SAPROPHYTIC ACID-FAST CULTURES

	Positive	Negative
Typical Cultures	11	0
Group I Cultures	0	12
Group II Cultures	0	3
Group III Cultures	3	7
Saprophytic Cultures	0	4

b. Group I—Growth from these cultures also gave rise to cream-colored, discrete colonies of typical appearance which, however, became lemon-yellow after 24 hours exposure to light at room temperature.

c. Group II—Cultures of these strains gave rise to white, beige, or buff to yellowish confluent growth with little or no tendency to form discrete colonies and there was no acquisition of pigment after light exposure.

d. Group III—These cultures produced a brilliant orange pigmentation of the colonies which tended to grow luxuriantly and to become confluent. The pigmentation appeared during incubation in the dark and was not modified by exposure to the light.

2. *Cellular Morphology*

An analysis of the characteristics of the cellular forms seen in Kinyoun stained smears of liquid cultures of the strains included in this study was found to be of value only in differentiating between typical and atypical organisms. The differences encountered among the various atypical strains did not seem to be sufficiently uniform among themselves to permit them to be used as distinguishing criteria. However, in all instances, the differentiation between typical and atypical strains was possible. The following summary details these observations:

a. Typical—On gross inspection these smears were blue in color, although on microscopic examination the individual bacilli were acid-fast. Definite cording was always found and the cells appearing rod-like and measuring 2 to 3.5 micra in length by about 0.5 micra in width.

b. Group I—On gross inspection these smears were red so that they

TABLE IV
DRUG SUSCEPTIBILITY OF CULTURES OF TYPICAL AND ATYPICAL ACID-FAST BACILLI

	Amount of Growth*	SM mcg/ml. 3	10	100	PAS mcg/ml. 0.1	1.0	10	INH mcg/ml. 0.2	1.0	5.0
	+	3	1	0	0	0	0	1	0	0
Typical	±	7	5	4	9	7	5	5	5	2
Cultures (11)	0	1	5	7	2	4	6	5	6	9
Group I	+	12	7	2	12	8	0	7	1	1
Atypical	±	0	5	7	0	4	12	5	10	10
Cultures (12)	0	0	0	3	0	0	0	0	1	1
Group II	+	2	1	0	3	2	2	3	2	2
Atypical	±	1	2	3	0	1	1	0	1	1
Cultures (3)	0	0	0	0	0	0	0	0	0	0
Group III	+	7	3	0	10	8	2	9	1	1
Atypical	±	3	7	8	0	2	8	1	7	6
Cultures (10)	0	0	0	2	0	0	0	0	2	3

*+ = Growth equal to that of control.
± = Growth present but less than that seen in control.
0 = No growth.

could be readily differentiated from those of typical organisms. As would be expected, the individual bacilli were highly acid-fast. The individual Group I cultures varied from those showing no cords to some with definite cording. In eleven of the cultures the cells varied in length from 1.5 to 3 micra and frequently were noted to contain granules giving rise to a banded appearance. However, one of the Group I cultures had cells which were as long as 10 micra and presented a bizarre banded appearance.

c. Group II—The staining properties of these cultures were identical with those noted in the Group I strains. However, the Group II cultures showed a slight tendency to form cords. The individual cells measured 2-3.5 micra in length and no granules were seen.

d. Group III—Smears of these cultures stained intensely red and resembled the other atypical cultures in this respect. The cells clumped together showing almost no evidence of cording. The individual cells had polar granules which tended to give them a dumbbell shaped appearance. They appeared shorter and stubbier than typical bacilli, measuring 1.5 to 2 micra in length by 0.5 micra in width.

3. *Rate of Growth in Liquid Medium*

As demonstrated in Figure 1, all categories of atypical bacilli had a very short latent period reaching an arithmetic phase of growth in less than 24 hours. The cultures of typical tubercle bacilli had the expected latent period of almost four days before growth was well established. At 48 hours it was possible to distinguish clearly between the typical and the atypical strains on the basis of the initial rates of growth as measured turbidimetrically and this is shown in Figure 1.

Culture number nine, a Group I atypical, was the only exception to this observation in that it had a very long latent period resembling a typical strain, in this respect. However, subsequent subcultures of strain number nine demonstrated rapid growth within 24 hours. Repeated subcultures of the typical strains failed to change their basic growth pattern and in no instance was the initial latent period shortened.

4. *Oxidation-Reduction of Dyes*

The results of these tests are summarized in Tables I and II. The typical cultures failed to reduce the dyes with one exception in which partial reduction was observed. The atypical cultures reduced the dyes completely or partially in 45 out of 50 tests (90 per cent). The known saprophytes completely reduced both dyes in all instances. Thus, the results of the oxidation-reduction tests, utilizing indophenol sodium and dibromoindophenol sodium respectively, were of value in differentiating the various cultures studied. The results obtained appeared to be consistent within the various categories tested in somewhat more than 90 per cent of the strains studied.

5. *Neutral Red Test*

The results of these tests are summarized in Tables I and III and it can be seen that they were of considerable value in differentiating the typical from the atypical cultures. All of the typical cultures of tubercle bacilli were

found to give a positive reaction to the neutral red test. On the other hand, 22 of the 25 atypical cultures demonstrated negative neutral red tests. All of the known saprophytes (M. phlei, M. butyricum, M. smegmatis, and M. ranae), included for comparison, gave a negative reaction to the neutral red test. Thus, these results are in general conformity with those obtained in the oxidation-reduction tests. In both the neutral red and oxidation-reduction tests, the results obtained suggested that the typical cultures reacted quite uniformly and in fairly clear contradistinction to the response of the atypical strains which more closely followed the reactions manifested by the saprophytic organisms.

6. *Catalase Reaction*

The results of the catalase tests are summarized in Table I. In general, the typical cultures tended to give less pronounced catalase reactions than

TABLE V

RESPONSE OF GUINEA PIGS INOCULATED WITH 1.0 mg. WET WEIGHT OF CULTURES OF TYPICAL AND ATYPICAL ACID-FAST BACILLI

		Animals Dying Before 6 Weeks					Animals Sacrificed at 6 Weeks				
			Mantoux Test					Mantoux Test			
	Route	Number	Positive	Negative	Typical Lesions	Positive Smears	Number	Positive	Negative	Typical Lesions	Positive Smears
Eleven											
Typical	IP (11)	8	5	3	8	8	3	3	0	3	3
Cultures	SQ (11)	6	4	2	6	6	5	5	0	5	5
TOTAL		14	9	5	14	14	8	8	0	8	8
Twelve											
Group I	IP (12)	6	1	5	6	6	6	6	0	6	5
Cultures	SQ (12)	1	0	1	1	1	11	10	1	9	9
TOTAL		7	1	6	7	7	17	16	1	15	14
Three											
Group II	IP (3)	3	3	0	3	3	0	0	0	0	0
Cultures	SQ (3)	3	3	0	3	3	0	0	0	0	0
TOTAL		6	6	0	6	6	0	0	0	0	0
Ten											
Group III	IP (10)	2	0	2	0	0	8	5	3	3	1
Cultures	SQ (10)	2	0	1	2	1	8	6	2	6	2
TOTAL		4	0	3	2	1	16	11	5	9	3

did the atypical strains. Thus, 23 out of the 25 atypical cultures demonstrated maximum catalase activity while none of the typical strains did so.

7. Drug Sensitivity

The data obtained regarding the sensitivity of the typical and atypical strains to the standard antituberculous drugs are summarized in Table IV. It can be seen that the typical cultures manifested varying degrees of resistance to the drugs tested and, in this respect, conformed with the patterns of sensitivity normally encountered in our hospital experience with retreatment cases of tuberculosis. None of the typical cultures demonstrated complete resistance to streptomycin, isoniazid, or PAS at the highest concentration tested. In general, the atypical cultures were more resistant to all of the drugs and no instances of complete sensitivity to any single agent were observed among them. Furthermore, no single group of the atypical cultures was found to be directly correlated with resistance to any specific antituberculous drug. The atypical cultures of all groups appeared to be more highly resistant to PAS than to the other two drugs tested.

8. Guinea Pig Inoculation

The results of the virulence studies on guinea pigs are summarized in Table V. It can be seen that most of the guinea pigs injected with standardized inocula of typical cultures of tubercle bacilli died within six weeks from the time of inoculation. They lost weight and those that survived long enough developed tuberculin sensitivity. Lesions grossly characteristic of tuberculosis were seen in all of these guinea pigs at autopsy and smears made of involved tissues were uniformly positive for typical acid-fast bacilli. Furthermore, we noted that the cultures comprising our Group II classification gave rise to similar results on guinea pig inoculation with those we obtained from the typical strains. Thus, the eleven typical cultures and the three atypical Group II strains demonstrated identical patterns of guinea pig virulence both on intraperitoneal and subcutaneous inoculation. These results are quite different from those obtained with the other atypical acid-fast organisms.

The Group I atypical cultures did not appear to be as virulent for guinea pigs as were the typical and Group II strains. Employing equivalent dosage we found that the six out of the 12 guinea pigs inoculated intraperitoneally with the Group I cultures died within six weeks while 11 out of the 12 animals injected subcutaneously survived the full 42 day period. However, at autopsy, lesions grossly characteristic of tuberculosis were seen in 22 out of 24 guinea pigs injected with Group I atypical cultures and smears of the involved tissues were usually positive for acid-fast bacilli. It was our opinion that the guinea pigs injected intraperitoneally with Group I strains showed greater involvement of the omentum and serosal tissues than did the animals receiving similar inoculations of typical cultures. However, it can be seen that in two instances, the Group I atypical cultures failed to produce obvious progressive disease beyond the site of inoculation in the guinea pigs.

On the other hand, the Group III atypical cultures were even less virulent as manifested by their decreased tendency to produce progressive disease in guinea pigs. Sixteen out of 20 of the animals with Group III strains survived six weeks and, at autopsy, none showed more than minimal involvement of the spleen. The guinea pigs which were inoculated subcutaneously, in addition, had local abscesses visible at the site of injection. In no instance was a guinea pig inoculated with a Group III culture found to have widely disseminated disease. However, of the 16 animals surviving six weeks after inoculation with Group III cultures, 11 were found to be tuberculin positive.

The guinea pig tests seemed to be conclusive in demonstrating a gradation in virulence among the acid-fast organisms tested. The typical cultures and Group II strains appeared to be equally virulent for guinea pigs. However, the Group I atypical cultures seemed to be somewhat less virulent, while the Group III strains appeared to be least capable of producing progressive or fatal disease.

9. *Clinical Course*

Careful analysis of the records of the patients from which the typical and atypical cultures were obtained suggested certain general correlations which appeared to be consistent (Tables I and VI). The 11 patients who were the sources of the typical cultures, never produced Group I or II organisms in many cultures taken of sputum, pharyngeal secretions, or gastric contents. However, two of these patients did produce Group III cultures late in the course of their disease. In addition, these 11 patients all had the classical pulmonary lesions of tuberculosis. From eight of these patients surgical specimens were obtained, all of which were positive on culture for typical human type tubercle bacilli. The disease encountered in these patients ranged from minimal to far advanced and no other disease process was either suspected or detected.

The 12 patients from whom the Group I atypical cultures were obtained all manifested disease which was clinically indistinguishable from classical pulmonary tuberculosis and ranged in character from minimal to far advanced. It has been our impression that the far advanced cases with Group I infections responded less well and more slowly to chemotherapy than did

TABLE VI

X-RAY CLASSIFICATION OF PULMONARY DISEASE ENCOUNTERED IN PATIENTS

	Typical	Group I	Group II	Group III
Minimal	3	3	....	2
Moderately Advanced	....	3	1	2
Far Advanced	8	6	2	5
Questionable	....	....	....	1
TOTAL	11	12	3	10

comparable patients from whom typical tubercle bacilli were recovered. However, this difference to some extent may be accounted for by the trend toward higher drug resistance demonstrated by the Group I cultures. Seven of the patients with Group I infections were operated upon and the pathological specimens all demonstrated the typical histological findings diagnostic of tuberculosis except for one patient whose pulmonary tissues demonstrated only non-specific chronic inflammation. However, this patient was highly sensitive to tuberculin (O.T. 1:10,000). All of the surgical specimens were positive on culture for Group I atypical organisms. It should be pointed out that the 12 patients from whom the Group I photochromogens were isolated never produced typical virulent tubercle bacilli on culture.

Group II cultures, characterized by rapid confluent growth, were obtained from only three patients and no surgical or autopsy specimens were available for study. These three patients were always consistent in their production of Group II cultures and at no time were their cultures positive for typical tubercle bacilli or acid-fast chromogens. Clinically, the disease seen in two of the patients was classified as far advanced and in the third case it was moderately advanced (Tables I and VI). The disease seen in these patients was indistinguishable from pulmonary tuberculosis caused by typical organisms. It was our impression that, although all three of these patients improved on conventional chemotherapy regimens, their general response was much slower and less striking than would have been anticipated in comparable cases infected with typical organisms.

The 10 strains of Group III atypical organisms were all characterized by their ability to form an orange pigment independent of light stimulus in the colonies grown on solid media. These organisms were obtained from either sputum, pharyngeal, or gastric cultures. An analysis of the clinical records of the 10 patients from whom the Group III organisms were isolated confirmed our impression that these particular atypical strains as a rule were isolated only from patients who had prolonged clinical courses and, in all but two instances, been on long-term chemotherapy. In no instance was a Group III strain isolated from a patient with only fresh disease. In the great majority of cases, these organisms were recovered from patients who originally had only typical tubercle bacilli in their cultures and then had become culture negative for a period of time after which the Group III isolation would occur. In our experience, Group III cultures never have initiated progressive, active pulmonary tuberculosis. Three of the patients from whom Group III cultures were obtained had pulmonary resections in the course of their hospitalization and in each instance the typical lesions of tuberculosis were found in the surgical specimens.

Discussion

The benefits derived from the increasing use of effective cultural techniques for the isolation of tubercle bacilli have been great, both in terms of greater diagnostic accuracy and also in the proper evaluation of therapy. However, the more frequent use of such techniques has also created a

practical problem related to the apparent increased frequency with which atypical acid-fast organisms are being isolated from patients. In many cases it is difficult to evaluate the significance of these atypical mycobacteria and, too frequently, there has been the temptation to regard them as non-pathogenic.[3, 4, 6, 11, 23]

During the past several years we have noted that approximately one-fourth of our patients had cultures reported positive for atypical acid-fast bacilli at one time or another in their clinical course. Careful observation of these atypical cultures promptly led us to certain impressions concerning their significance and relationship to the pulmonary disease found in the patients from whom they were isolated. Therefore, it seemed important to set up a study in which the biological characteristics of representative strains of these atypical organisms were compared with those of cultures of typical, human type tubercle bacilli isolated under similar conditions.

Cursory inspection of the atypical acid-fast cultures obtained from our patients indicated that they were readily separated into three groups on the basis of their growth on solid media. The strains which gave rise to typical colonies which became pigmented on exposure to the light (photochromogenic) were included in Group I. The strains which formed confluent, diffuse growth on solid media and did not become pigmented on exposure to light were included in Group II. Finally, the Group III strains consisted of cultures which grew luxuriantly on solid media and produced an orange pigmentation in the dark (skotochromogenic).

In general, the atypical strains studied revealed sharp differences in their behavior in terms of cellular and colonial morphology, biochemical reactions, and pathogenicity for guinea pigs as compared to the typical cultures. However, as would be expected, the individual variations were great and, in terms of any specific test, there was considerable overlapping so that it was not possible to separate completely the typical from atypical cultures on the basis of any single reaction. Actually, the original classification based upon colonial morphology appeared to be as valid as that derived on any other basis. These results are not surprising when one considers the wide range of variations which have been recognized in the morphology, biochemical reactions, and virulence of human type tubercle bacilli.[24, 25]

In our experience, Group I atypical acid-fast cultures have always been isolated from patients with disease which is clinically and pathologically identical with tuberculosis. In these patients it has been the only organism recovered from their sputum and in untreated cases it always has been associated with progressive, invasive disease. Although these strains, in general, have shown increased resistance to the standard antituberculous drugs, not all cultures are highly resistant to any single chemotherapeutic agent. Thus, it seems unlikely that these strains can be related to the acquisition of resistance to either streptomycin, PAS, or isoniazid.

Cultures classified by us as Group II atypical acid-fast strains are quite rare in our experience. However, when present, they are associated with progressive disease clinically indistinguishable from classical tuberculosis.

The patients from whom Group II cultures have been obtained never produce any other type of acid-fast bacilli nor do we believe that the presence of such atypical organisms can be correlated with resistance to any single antituberculous drug.

On the other hand, our experience suggests that the Group III atypical organisms are much less clearly related to the presence of active, invasive pulmonary tuberculosis than are either Group I or Group II strains. At no time have we isolated a Group III culture from a patient who did not have evidence of old, relatively stable and quiescent disease of long clinical duration and who had, in the majority of instances, received a long course of chemotherapy. As a rule, the patients from whom Group III organisms were obtained had previous isolations of typical or, in a few cases, Group I strains from cultures taken earlier in the course of their disease. At the present time, however, we feel that the cultures classified by us as Group III are much less homogenous in all respects than are the other types of atypical organisms reported. In general, it is our impression that the majority of Group III isolations occur in patients shortly before they become definitely culture negative. It is noteworthy that our efforts to recover such organisms from individuals known to be free from pulmonary tuberculosis have always failed.

At the present time we can offer no logical explanation to account for our experience with the Group III organisms. We cannot escape the conclusion that the isolation of such an organism bears a significant relationship to previously active pulmonary tuberculosis but we can find no suggestion in our patients or their contacts to support the classification of the Group III acid-fast bacilli as highly pathogenic mycobacteria. The absence of significant resistance to any single antituberculous drug on the part of the Group III cultures makes it difficult for us to believe they can be accounted for on the basis of their being drug-resistant mutants or variants. However, at present this possibility cannot be eliminated entirely.

Our experience has convinced us that the isolation of Group I or Group II cultures from a patient must be considered meaningful and should be regarded as a definite indication for the initiation of antituberculous chemotherapy. This recommendation is made in spite of the fact that our experimental results clearly reveal that Group I and Group II cultures show growth and biochemical characteristics approaching or identical to those of known acid-fast saprophytes. However, the results of guinea pig inoculation certainly suggest that cultures of these two groups are virulent. This view, of course, is even more strongly supported by the characteristics of the disease encountered in the patients from whom these cultures were isolated. Therefore, we believe that the confirmed isolation of either Group I or II cultures is an immediate and proper justification for chemotherapy and for a diagnosis of tuberculosis. In terms of our present knowledge we feel that it would be unfair and imprudent to withhold a diagnosis of tuberculosis from those patients consistently yielding such atypical organisms on culture in association with clinical evidence of disease.

The Group III cultures that we have encountered appear to have definite

significance in terms of the biological history of tuberculosis in the individuals from whom they are isolated. In general, we feel that the presence of such atypical cultures is a good prognostic omen; however, inasmuch as the majority of these patients were culture-positive for typical organisms in their immediate past, we feel that full and adequate chemotherapy should be continued in these patients until the traditional criteria for cessation of treatment are fulfilled plus complete absence on repeated culture of the Group III bacilli.

We have observed a few individuals who were positive for Group III cultures on the occasion of their initial diagnostic workup. It is our opinion that these patients should receive full courses of chemotherapy if they have any pulmonary pathology detectable. If no evidence of clinical disease can be found, such patients must be most carefully observed and re-evaluated at frequent intervals.

SUMMARY

The characteristics of 25 atypical and 11 typical cultures, obtained from 36 patients with pulmonary tuberculosis, were studied in terms of: 1) Colonial and cellular morphology; 2) Rate of growth in liquid medium; 3) Drug sensitivity; 4) Oxidation-reduction of dyes, catalase reaction, and neutral red tests; 5) Guinea pig virulence; and 6) The characteristics of the clinical disease encountered in these cases.

We were able to classify the atypical organisms as follows: Group I, consisting of 12 cultures which produced typical colonies and developed lemon-yellow pigmentation on exposure to light (photochromogenic); Group II, comprising three cultures which produced confluent growth with little tendency to form discrete colonies and showed no pigmentation; and Group III, consisting of 10 cultures which produced yellow-orange colonies in the dark (skotochromogenic). In general, the atypical organisms showed a rapid rate of initial growth in liquid Dubos medium, complete or partial reduction of the oxidation-reduction dyes, highly positive catalase reactions, and negative neutral red tests. Guinea pig inoculation revealed that Group I and II strains were virulent. The Group III organisms, however, were uniformly much less virulent. The atypical cultures were not markedly different from the typical strains in their sensitivity to streptomycin, PAS and isoniazid.

Review of the clinical records of the 25 patients from whom the atypical cultures were isolated, suggested certain correlations. The 15 infected with Group I and II strains all had significant pulmonary disease, clinically indistinguishable from tuberculosis caused by typical organisms, and at no time in their clinical course were cultures of typical organisms obtained. These 15 patients responded more slowly to chemotherapy than did those infected with typical strains. The 10 Group III strains all were isolated from patients with long-standing pulmonary tuberculosis who had responded satisfactorily to chemotherapy and from whom typical organisms had been recovered in sputum cultures obtained during the earlier phases of their disease. The Group III strains did not cause progressive

disease in any patient. Furthermore, recovery of Group III strains was rarely followed at a later time by the isolation of typical cultures from the same patient.

RESUMEN

Se estudiaron las características de 25 cultivos atípicos y 11 típicos obtenidos de enfermos de tuberculosis pulmonar en relación con: 1) Morfología celular y de las colonias; 2) Proporción de crecimiento en medio líquido; 3) Sensibilidad a las drogas; 4) Oxidación-reducción de colorantes, reacción de la catalasa y del rojo neutro; 5) Virulencia para el cuy y 6) Las características de la enfermedad clínica en estos casos.

Podemos clasificar los organismos atípicos como sigue: Grupo I, consistente en 12 cultivos que produjeron colonias atípicas y presentaron pigmentación amarillo limón al exponerse a la luz (fotocromogénicos) Grupo II, que comprende tres cultivos que produjeron crecimiento confluente con poca tendencia a hacer colonias discretas y no mostraron pigmentación; y Grupo III, de diez cultivos que produjeron colonias pigmentadas amarillo naranja en la obscuridad (escotocromogénicos). En general los organismos atípicos mostraron un rápido crecimiento inicial en medio líquido de Dubos, reducción completa o parcial de los colorantes de la oxidación-reducción, reacciones altamente positivas de la catalasa, y reacciones negativas del rojo neutro. La inoculación al cuy reveló que los grupos I y II eran virulentos. Sin embargo el grupo III fueron uniformemente menos virulentos. Los cultivos atípicos no fueron notablemente diferentes de los típicos en cuanto a su sensibilidad a la estreptomicina, PAS e isoniacida.

La revisión de los expedientes clínicos de 25 enfermos de quienes se aislaron cultivos atípicos, sugirieron ciertas correlaciones.

Los 15 infectados con el grupo I y II tenían todos enfermedad pulmonar franca, que no se podía distinguir de la tuberculosis causada por la cepas típicas, y en ningún tiempo de su evolución clínica se obtuvieron cultivos típicos de ellos. Estos 15 enfermos respondieron más lentamente a la quimioterapia que los infectados con cepas típicas.

Los 10 del grupo III fueron aislados de enfermos con tuberculosis de larga duración que habían respondido satisfactoriamente a la quimioterapia y de quienes se habían obtenido organismos típicos en fases anteriores de su enfermedad.

El grupo III no causo enfermedad progresiva en ningún enfermo.

Más aún, el hallazgo de cepas III rara vez fué seguido más tarde de aislamiento de cepas típicas en el mismo enfermo.

RESUME

Les caractéristiques de 25 cultures atypiques et II cultures typiques, obtenues d'après 36 malades atteints de tuberculose pulmonaire, ont été étudiées sur les bases suivantes:

1) morphologie cellulaire et morphologie de la colonie;

2) taux de croissance en milieu liquide;

3) sensibilité à la médication;

4) oxydation-réduction des colorants, réaction à la catalase, et tests au rouge neutre;

5) virulence sur le cobaye;

6) caractéristiques de la maladie clinique rencontrée dans ces cas.

L'auteur put classer les germes atypiques comme il suit: Groupe I, qui comporte 12 cultures qui produisirent des colonies typiques et donnèrent lieu à une pigmentation jaune-citron à l'exposition à la lumière (photochromogéniques); Groupe II, qui comprend trois cultures qui montrèrent une croissance confluente, avec une petite tendance à la formation de colonies discrètes et qui ne produisirent aucune pigmentation; Groupe III, consistant en 10 cultures, qui formèrent des colonies jaune orange à l'ombre (skotochromogéniques). En général, les microbes atypiques montrèrent un taux rapide de croissance initiale en milieu liquide de Dubos, une réduction complète ou partielle de l'oxydation-réduction des colorants, des réactions à la catalase hautement positives, et des tests au rouge neutre négatifs. L'inoculation au cobaye révéla que les souches des groupes I et II étaient virulentes. Les microbes du groupe III cependant, furent uniformément moins virulents. Les cultures atypiques ne purent pas nettement se différencier des souches typiques par leur sensibilité à la streptomycine, à l'acide para-aminosalicylique, et à l'isoniazide.

La revue des rapports cliniques concernant les 25 malades chez qui les cultures atypiques furent isolées, évoque certaines corrélations. Les 15 malades infectés avec des souches des groupes I et II avaient une atteinte pulmonaire importante, cliniquement indiscernable de la tuberculose causée par des germes typiques, et à aucun moment de leur évolution clinique on ne put obtenir des cultures de germes typiques. Ces 15 malades répondirent plus lentement à la chimiothérapie que ceux infectés par des souches typiques. Les 10 souches du groupe III furent toutes isolées chez des malades atteints de tuberculose pulmonaire datant de longtemps, qui avaient répondu favorablement à la chimiothérapie, et chez qui les bacilles typiques avaient été recueillis dans les cultures d'expectoration obtenues pendant les phases précoces de leur affection. Les souches du Groupe III ne furent cause d'aucune atteinte extensive chez les malades. En outre, après avoir recueilli des souches du groupe III, rarement chez le même malade furent isolées ensuite des cultures typiques.

ZUSAMMENFASSUNG

Die Charakteristika bei 25 atypischen und 11 typischen Kulturen, die von 36 Patienten mit Lungentuberkulose gewonnen wurden, wurden untersucht unter Berücksichtigung von: 1) Morphologie von Kolonien und Zellen; 2) Wachstumsrate in flüssigen Nährböden; 3) Arzneimittel-Empfindlichkeit; 4) Reduktion von Farbstoffen durch Oxydation, Katalase-Reaktion und Neutralrotproben; 5) Meerschweinchen-Virulenz; und 6) die Charakteristika der bei diesen Fällen vorliegenden klinischen Erkrankung.

Wir vermochten die atypischen Organismen wie folgt zu klassifizieren: Gruppe I, bestehend aus 12 Kulturen, die typische Kolonien bildeten und eine zitronengelbe Pigmentierung hervorbrachten nach Licht-Exposition (photochromogen); Gruppe II umfasst 3 Kulturen, die ein konfluierendes Wachstum bewirkten mit geringer Tendenz zur Bildung diskreter Kolonien, und die keine Pigmentierung zeigten; und Gruppe III, bestehend aus 10 Kulturen, die im Dunkeln orangegelbe Kolonien bildeten (skotochromogen). Im allgemeinen zeigten die atypischen Organismen eine schnelle anfängliche Wachstumsrate in Dubos' flüssigem Nährboden, eine komplette oder partielle Reduzierung der durch Oxydation reduzierenden Farbstoffe, stark positive Katalase-Reaktionen und negative Neutralrotproben. Meerschweinchen-Impfungen ergaben, dass die Stämme der Gruppe I und II virulent waren. Einheitlich waren die Organismen der Gruppe III jedoch erheblich weniger virulent. Die atypischen Kulturen differierten nicht entscheidend gegenüber typischen Formen in ihrer Sensibilität auf Streptomycin, PAS und INH.

Eine Durchsicht der klinischen Aufzeichnungen der 25 Kranken, von denen die atypischen Kulturen gewonnen wurden, lassen gewisse Beziehungen vermuten. Die 15 Träger von Stämmen der Gruppe I und II hatten sämtlich eine beträchtliche Lungenerkrankung, die klinisch nicht zu unterscheiden war von einer durch typische Organismen verursachten Tuberkulose, und zu keiner Zeit ihres klinischen Verlaufs ergaben sich Kulturen mit typischen Organismen. Diese 15 Patienten reagierten langsamer auf die Chemotherapie als die mit typischen Stämmen infizierten Fälle. Die 10 Stämme der Gruppe III wurden sämtlich gewonnen von Patienten mit lang bestehender Lungentuberkulose, die befriedigend auf die Chemotherapie reagiert hatten und bei denen typische Organismen in Sputumkulturen gefunden worden waren, die man während früherer Phasen ihrer Krankheit angelegt hatte. Die Stämme der Gruppe III verursachten bei keinem Kranken eine fortschreitende Erkrankung. Darüber hinaus folgte dem Nachweis von Stämme der Gruppe III selten zu einem späteren Zeitpunkt die Isolierung von typischen Kulturen desselben Patienten.

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Considerations in Humidification by Nebulization*

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Nebulization may provide therapy by medication, humidification, or even by cooling. The use of nebulization for humidification has been widely proposed and accepted, but indications and requirements have not been established except by clinical impression, and knowledge of humidity is scant. The functions of medication as distinct from humidification have been confused.

The purpose of this paper is threefold:

1. To show the rational indications and requirements for humidification that can be derived from a consideration of both the available data and the physical processes involved in respiratory tract air conditioning.

2. To present data on the production of vapor and liquid humidity by nebulizers operated under various circumstances and to show the effect of temperature and other variables.

3. To describe a method of nebulization which provides adequate humidity for continuous intermittent positive inspiratory pressure breathing.

Humidity Terminology

In consideration of these matters, it is helpful to use an absolute humidity term having direct physiological meaning. Humidities are expressed in two principal ways. Relative humidity or per cent saturation at a given temperature expresses "dryness" *at that temperature,* while absolute humidity expressed on a dry air basis permits direct comparison of water content at different conditions. *Both* are required to fully express a given humidity.

The commonly used absolute humidity expressions such as "grams of water per cubic meter of dry air" or "grains of moisture per pound of dry air" are cumbersome and lack direct physiologic meaning. Walley[1] and Marshall[2] have used the term "per cent saturation at body temperature" to relate absolute humidities produced by their devices to the absolute humidity achieved in the body. Cole[3] used the expression "per cent water content of lung air." The shorter term "per cent body humidity"

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This study was supported in part by funds from the Dallas Heart Association.

Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.

(per cent B.H.) is proposed for this use and utilized in this paper. Body humidity is defined as the absolute humidity (water content) of saturated air at body temperature (37° C, 98.6° F, pH_2O of 47 mm. of Hg). Per cent body humidity is easily calculated from standard absolute humidity data, or by the equation:

$$\text{Per Cent B.H.} = \frac{pH_2O}{760\text{-}pH_2O} \times \frac{713}{47} \times 100.$$

For clinical purposes a simple ratio of $pH_2O/47$ gives values which are within 1.5 per cent B.H. of the true absolute humidity.

The Need for Humidification

A number of investigators have studied air conditioning in the respiratory tract. (Ingelstedt's recent paper[4] is a convenient source of reference to the available data.) The striking finding in all this work is that inspired air is so easily humidified in normal airways even under adverse circumstances. None of the data show significantly dry air reaching the trachea during nasal or even maximal oral respiration, although some observations suggest that warm air should be at above 70 per cent relative humidity to prevent incipient drying or alteration of mucosa near the inlet to the airways.[5, 6] In addition to the conditioning achieved in the upper airways, warming and humidification are easily completed by the larger surface available in the tracheo-bronchial tree. According to calculations from Rohrer's data,[7] the surface area of bronchi down to 1.5 mm. diameter amounts to about 700 sq. cm. as compared to about 220 sq. cm. in the nose and pharynx and 100 sq. cm. in the larynx and trachea. Thus, it would not be reasonable to assume that small bronchial "inspissated" mucus casts are caused by lack of humidity. However, it is well known from clinical experience that serious drying can occur.

Since none of the studies on air conditioning have included the disease states in which such drying is most likely, the indications for therapeutic humidification thus far must rest on inference and isolated observations. From the studies of normals, it is fairly obvious that some combination of excessively drying air and abnormal humidifying mechanism must be present for airway drying to occur. The drying tendency of air depends on its humidity, temperature, volume respired, and rate of flow past the mucosa. The humidifying ability of mucosa depends more on the mere presence of a film of moisture at the surface than on any other factor such as surface temperature or concentration of solute in the surface moisture. When normal secretions are present, the water vapor pressure driving the humidification process is essentially that of pure water at the surface temperature. If such free moisture is absent, vapor pressure at the dry surface is much lower. For instance, if a patient breathing through the mouth does not keep saliva spread over the surface, much drier air may reach the trachea than the data on oral respiration in normals would indicate. Factors such as dehydration, atropine-like drugs, and reflexes which affect secretory rate can contribute to lower airway drying if they result in grossly dry upper airway surfaces.

The most serious drying effects occur in the trachea. Since even grossly abnormal upper airways provide some humidification, drying usually occurs in the presence of thick tracheal exudate or with a tracheostomy. If thick exudate coats the mucosal surface, a barrier exists between the surface of the exudate and the moisture provided by mucosal secretion, and the surface becomes dry more easily. A dry surface in the trachea has a more serious effect than in the nose since all the tracheo-bronchial exudate and secretions must pass upward through the driest area, where the collection of exudate or secretion causes the drying process to be self-perpetuating and progressive. Precisely the expected thick, pasty exudate lining the trachea has been observed in comatose patients who have been hyperventilating through a dry mouth, following aspiration.

With tracheostomy, breathing room air often causes subjective discomfort, plugging of the tracheostomy tube, and drying and encrustation of exudate or secretions, even with an initially normal tracheo-bronchial tree. In the presence of thick exudate, drying can be disastrous. However, patients with permanent tracheostomy have surprisingly moderate difficulty in the absence of bronchopulmonary disease.

The humidity necessary to prevent ill effects of drying varies considerably. To prevent subjective symptoms caused by incipient drying in normal nasal passages, 70 per cent or more relative humidity at 20-27° C (say 25-45 per cent B.H.) should be sufficient, and less humidity is required at lower temperatures.[5] Air at 25° C and near 100 per cent relative humidity (49 per cent B.H.) further minimizes drying tendency at the inlet and is easily warmed and humidified to conditions which ordinary air reaches only at the hypopharynx or trachea.[3] The vapor pressure gradient between mucosal surface and air, which is at least about 20 mm. Hg for air at 20° C and 35 per cent relative humidity, is reduced to about half this value by saturated air at 25° C, and once such air has been warmed to about 34° and, say, 98 per cent relative humidity, the mucosal-air gradient is only a few mm. of Hg. Thus, saturated air at 25° C represents an approximate upper limit to the usefulness of humidity for nasal respiration, even when tracheal exudate is present. Slightly higher values might be desirable for oral breathing when tracheal exudate is present.

For tracheostomy breathing, the necessary humidity may range all the way from the same minimum conditions necessary to prevent discomfort or alteration of mucosa in the nose,[6] to the normal tracheal inlet conditions of near body temperature, and near 100 per cent saturation (near 100 per cent body humidity). High relative humidity seems more important than high temperature to prevent drying, since even at the same absolute humidity warmer air will result in a slightly higher mucosal temperature and thus increase the mucosa air pH_2O gradient.

When drying of tracheal exudate has already occurred, provision of maximum possible humidity is important, and the delivery of liquid water by mist therapy or instillation is helpful in rapidly remoistening the dry exudate. Delivery of maximum humidity implies that the air be saturated (or supersaturated) at near body temperature.

When tracheal exudate or secretions are a problem, medication has an important role in the therapy of drying. The administration of hygroscopic, wetting, and enzymatic agents can be expected to aid in the thinning and elimination of thick exudate and thus help restore normal mucosal humidifying efficiency. (Such agents are certainly indicated for therapy of inspissated material in the small bronchi where humidity is already at a maximum and cannot be increased by humidification of inspired air.)

The role of pure water mist in the therapy of tracheo-bronchial exudate when humidity is already near maximum is obscure. The addition of liquid water has no humidifying effect on a mucosa-exudate-air system which is all at near body temperature and 100 per cent relative humidity. Any action by liquid water must be a mechanical one, such as providing a vehicle for the liberation and evacuation of exudate. In the same way, droplets containing medication have no humidifying effect when the air is saturated at near body temperature, and when the air is not saturated the mere deposition of the droplets from the gas stream to the mucosa does not change the humidity. The therapeutic effect is mechanical or due to the medication.

The rational indications for therapeutic humidification of air which has an excessive tendency to produce drying seem to be one or more of the following:

1. The presence of subjective discomfort or the possibility of ill effect from incipient drying in the upper airways,

2. The presence of gross drying in the upper airways,

3. The admission of air directly to the trachea as in tracheostomy, and,

4. The presence of excessive, thick tracheobronchial exudate or the inability to move exudate and secretions rapidly through the trachea.

The amount of humidity required for therapy may vary from about 70 per cent relative humidity for warm air (less for cooler air) to saturation at near body temperature. Mist therapy providing "super saturation" *at near or above body temperature* has a definite role in the therapy of dried exudate, but in the presence of a moist surface and saturated air its therapeutic effect must be due to mechanical factors.

Medication has an important therapeutic role when exudate or secretions are a problem, but again, this should not be confused with humidification.

Nebulizer Humidity Production

Gas in the contacting chamber of a nebulizer, whether from the jet or that drawn in by aspiration, is saturated with water vapor almost instantly. This production of *vapor humidity* depends on temperature and is the same for all devices producing saturation at that temperature (neglecting changes in vapor pressure caused by solutes). This operating temperature of a nebulizer is always lower than the temperature of the surroundings, depending on the amount of evaporation and the surface area of the nebulizer.

In contrast, the amount of liquid humidity produced may vary considerably, depending more on particle size than number of particles. The range of particle size for high humidity is different from that for effective medication since large particles may evaporate from the surface of the apparatus or moisten upper airway mucosa, thus providing effective humidity but representing ineffective medication to the smaller bronchioles.

Alteration of nebulizer mist occurs because of warming in apparatus and in the patient's upper airways. These effects are different for humidity and medication. When pure water mist is warmed, the finer droplets evaporate rapidly, exchanging liquid for vapor humidity. When water vapor is added to the mist simultaneously with warming, as in the airways, pure water droplets may or may not evaporate. When airway mucosa is moist so that humidification efficiency is high in comparison to warming efficiency, the droplets should tend to persist. When the mist is warmed by radiation or dry mucosa decreases humidification efficiency, more evaporation of the droplets should occur. When solute is present, the droplets are "stabilized"[8] and do not completely evaporate on warming of the mist. Thus more droplets persist to be deposited in the tracheobronchial tree. As discussed in the previous section, a distinction should be made between humidification and the medicinal or mechanical effect of droplets deposited in the tracheobronchial tree.

The presence of solute in the nebulizer changes the production of vapor humidity by lowering the vapor pressure. Conversely, the production of humidity affects the rate at which medication is delivered. The vapor pressure lowering can be estimated by assuming that the ideal solution equations apply, in which case vapor pressure lowering is proportional to mol fraction of solute present. A commonly used nebulizer solution* contains 0.44 mol per cent $NaHCO_3$ and 1.1 mol per cent glycerine. A 10 per cent propylene glycol solution is 2.6 mol per cent. Thus initial vapor humidity lowering in such solutions amounts to about 0.02 times the humidity of pure water at the operating temperature. Concentration of the solute as the solution is nebulized increases at a rate which depends on the ratio of solute-free vapor to solute containing liquid produced. Nebulizers which may produce 1/3 of their humidity as vapor and 2/3 as liquid will concentrate to about 125-130 per cent of the initial concentration each time one half of the solution is nebulized. That is, concentration will rise from 2 per cent initially to about 2.5 per cent, 3.2 per cent, 4.1 per cent, etc., as 1/2, 3/4, 7/8, etc., of the solution is nebulized, respectively. The effect is not important in this case. However, if a nebulizer with a small liquid humidity production is heated to produce high vapor humidity, vapor humidity will amount to a large fraction of the total humidity. In such a case, the rise in concentration approaches that for no loss of solute from the solution. That is, 2 per cent initial will rise to about 4 per cent, 8 per cent, 16 per cent, etc., as 1/2, 3/4, 7/8, etc., of the solution is nebulized. At such higher concentrations many other factors may be

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operable. In any event, the vapor humidity and amount of medication produced will change markedly toward the end of nebulization of a given amount of solution; almost pure solute may be present if the nebulization is continued long enough.

Experimental Observations

Methods: To establish the magnitude of the humidity produced by nebulizers and to test the practical effect of some of the above factors, several different large and small nebulizers were tested at various flow rates and at room temperatures of 25-29° C, under the following circumstances:

1. Used directly, without intervening apparatus.

2. Used through a "mask" (3″ of 1 1/2″ rubber tubing) with rebreathing bag and non-return valve.

3. Used through 30″ of corrugated anesthesia tubing.

4. Directed into a sealed enclosure (plastic head tent) of about 3 cu. ft. capacity.

5. Recirculating air within the plastic head tent.

6. Directed into one nostril and out the other with the nasopharynx held closed.

The nebulizers tested were: Type (A) Mist-O_2-Gen "JR"; Type (B) NCG Model 24650; Type (C) NCG Model 24850; Type (D) Mist-O_2-Gen "SR"; Type (E) Vaponefrin (E_1 and E_2-Model "500," E_3-Model "Standard"); Type (F) Adrenomist; and Type (G) DeVilbis No. 40.

Total humidity of nebulizer output was measured by standard wet and dry bulb thermometry techniques[9] after warming the entire stream to above the dew point of the mist. Vapor humidity at any location was obtained from a temperature reading; liquid humidity at that location was the difference between total and vapor humidity. When the mist passed through apparatus before measurement, the difference represented *effective* liquid humidity since it did not include any un-evaporated liquid lost in the apparatus.

Observations were converted to per cent B.H. by first determining pH_2O from vapor pressure and psychometric data[10] and then using the relation between pH_2O and per cent B.H. explained above. Wet and dry bulb observations were initially checked by dew point readings; this was discontinued when general agreement was found. Reliability of the data was indicated by agreement within 1-2 per cent B.H. of several readings taken during long runs on the large nebulizers while warming of the output stream was varied so that wet-dry bulb difference ranged from 2-15° C.

Results: All the observations made are listed in Table I. Table II summarizes the ranges of liquid and total humidity encountered under the various circumstances of the study and compares these values with data on humidity produced by various devices recalculated from observations by previous investigators.

In Figure 1 the various humidities are plotted as per cent B.H. against operating temperature. The saturated vapor curve indicates the *vapor*

TABLE I
NEBULIZER HUMIDITY PRODUCTION

Nebulizer Type	Nebulizer No.		Nebulizer Operation: Flow Rate, L/Min. To Mixed	Flow Rate, L/Min. Jet	Temperature: Room	Temperature: At Nebulizer[A]	Temperature: At Delivery[A]	Humidity Produced, Per Cent B.H. Liquid Total: At Nebulizer[B]	Humidity Produced, Per Cent B.H. Liquid Total: At Delivery
					LARGE CONTINUOUS DUTY NEBULIZERS				
A	1 to 11	Direct	10	.... to	25.5 to 26.5	16 to 17		6 to 23	35 to 52
		Direct	10	....	26.0	16.5	....	14	 43
			15	....	27.5	15.3	....	10	 37
	4	Tube	15	....	27.0	15.0	19.1	(12)	5 38
			15	15	26.2	14.0	17.1	(9)	4 33
			15	30	27.0	14.0	16.1	(8)	4 32
			15	45	27.0	13.5	15.5	(5)	2 29
			15	70	27.0	13.1	15.1	(3)	0 26
			15	R.A.	27.0	16.1	17.2	(3)	1 31
		Recirculating	10	R.A.	25.7	22.5	23.8	(6)	2 48
			15	R.A.	25.7	22.0	23.5	(6)	2 47
B		Tube	15	....	27	15.5	19.8	(19)	11 46
			20	....	26.5	14.3	17.8	(12)	6 37
			30	....	25.5	12.9	16.1	(10)	5 33
		Tent via Tube	15	....	26	19.5[C]	25.0	(14)[C]	0 49
			20	....	26	18.0[C]	24.3	(15)[C]	0 47
			30	....	26	16.0[C]	23.4	(16)[C]	0 44
C		Tube	15	....	26.5	15.0	19.7	(22)	13 48
		Tent	15	....	27.0	15.5	24.7	(22)	1 49
D			9	....	25.5	18.5	22.0	(26)	17 58
		Tube	10	R.A.	25.5	18.9	21.0	(24)	20 57
			5.0	R.A.	25.0	20	22.6	(21)	15 51
		Tent	10	....	25.5	18.6	25.0	(18)	2 51
					SMALL NEBULIZERS				
E	2	Direct	5	....	28.0	15.2	....	44	 70
	1		8	....	29.0	15.5	....	57	 84
	2		13	....	28.7	15.5	....	54	 81
	3		13	....	28.5	13.9	....	49	 73
	2	Mask	11	....	29.5	....	17.5	....	10 41
	3		11	....	29.5	....	17.8	....	9 40
	2	Tube	11	....	29.0	13.0	22.3	(57)	38 80
	3		11	....	28.7	12.5	22.2	(54)	35 76
	2	Tent	9	....	27.0	14.0	25.0	(34)	9 58
	2	[D]	11	....	....	12.3	13.5	(55)	 77
F		Direct	16	....	28.5	13.5	....	26	 50
		Mask	16	....	29.0	....	17.5	....	5 36

TABLE I: NEBULIZER HUMIDITY PRODUCTION—Continued

G	Direct	20	....	28.5	13.2	....	21	....	48
1	Tube	17	....	28.7	13.0	20.0	(31)	18	54
	Mask	3	....	29.0	....	17.3	....	23	53
		16	....	29.0	....	16.7	....	20	49
		20	....	29.0	....	16.0	....	18	46
	Tent	12	....	26.5	14.2	24.5	(26)	4	51
		16	....	26.5	13.4	24.3	(28)	5	52
		20	....	26.5	12.7	24.0	(28)	4	50
2	Direct	10	....	31	15.5	....	29	....	56
	Nasal[E]	10	....	31	15.5	31.2[E]	....	8[E]	76[E]

[A]—Read vapor humidity from Fig. 1.
[B]—Brackets indicate effective liquid humidity.
[C]—R.A.—Room air admixed.
[D]—Directed through nebulizer Type A.
[E]—Directed through the nostril; output measured from other nostril.

TABLE II
RANGE OF HUMIDITY VALUES

Device and Operation		Gas Flow Rate L/Min.	Operating Temperature °C	Warming in Apparatus °C	Liquid Humidity At Nebulizer % B.H.	Liquid Humidity At Delivery % B.H.	Liquid Humidity Total Humidity % B.H.
Nebulizer Direct	(A 1-11)	10-15	15-17		6-23		35-52
	(D,F,G)	5-20	13-15	....	21-57	....	48-84
Nebulizer by Tube	(A,B,C,D)	15-85	13-20	1-5	3-26	0-20	26-58
	(E,G)	11-16	12-13	7-10	31-57	18-38	5480
Nebulizer Through "Mask"	(E,F,G)	11-20	....	4-5	....	5-23	36-53
Nebulizer Into Tent	(B,C,D)	10-30	15-19	To near	14-22	0-2	44-51
	(E,G)	9-20	13-14	Room temp.	26-34	4-9	50-58
Nebulizer Recirculating	(A)	10-15	22	To near Room. temp.	6	2	47-48
Nebulizer Through Nose	(G)	10	15.5	15.7	29	8	....
"Natural fog"[11]			24			5-17	51-63
Nebulizer in Incubator[12]			31-32			3-11	79-83
Airway "Exchanger"[13]			26-27			?	70-80
Water evaporator[1]		35-20	49			0	80-89
Oxygen bubblers[10, 1]		3	46			0	60-70 R.H.*
						0	86

*R.H. = Relative Humidity.

humidity at any operating temperature; whereas data on total humidity is indicated by the various lines and points. The height of the total humidity above the vapor curve indicates the *liquid humidity*. The lined area of Figure 1 represents all the data for actual or effective liquid humidity production at the nebulizer except for nebulizer type (E) which is represented by the points high above the curve. With this exception, total humidity production was about 30-60 per cent B.H. and liquid humidity about 5-30 per cent B.H. The points near the vapor curve at 25° C represent the values sampled from the tent as well as data from the literature on "natural fog" in a room,[11] the points at 31.5° C are the data from the literature on incubator mist content.[12] It will be noted that the amounts of liquid humidity are ordinarily small in relation to 100 per cent B.H., although they provide an important increase over the vapor humidity that can be obtained at comfortable room temperatures. Therefore, variations in mist production are not as significant as might be expected in the production of near body humidity; operating temperature is a more important variable. The extension of the line in Fig. 1 representing mist containing 15 per cent liquid humidity is based on the assumption that liquid content is independent of operating temperature. The general validity of this assumption is confirmed by the observation that mist production from a heated nebulizer seems to be as copious as that from an unheated nebulizer. The vapor humidity curve and such a line representing additional liquid humidity permit estimation of the temperature to which a nebulizer must be heated to provide near body humidity. Fig. 1 also provides a convenient means

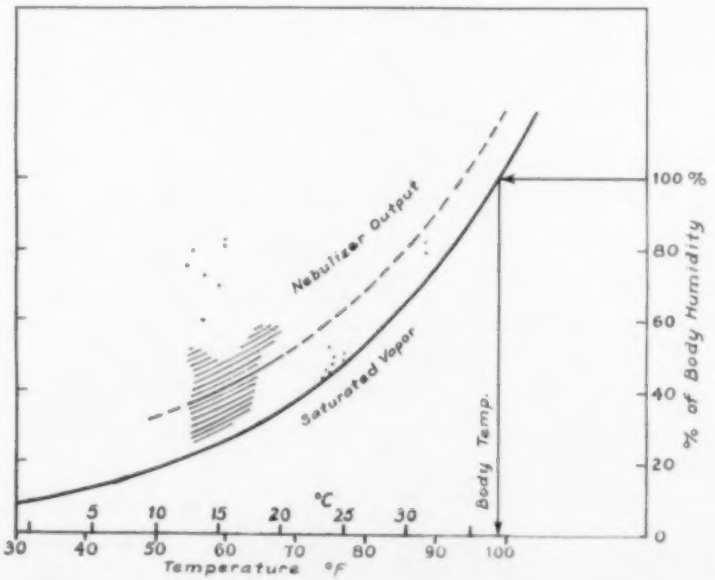

FIGURE 1: Humidity—Temperature relations for nebulization of H_2O.

of visualizing other humidities. The per cent B.H. of any air is obtained by multiplying the value from the saturated vapor curve at the temperature of the air by the fractional relative humidity.

Discussion

Except for nebulizer type (E), very little loss in humidity resulted from baffling or raining out in the tube or tent. This is shown by a few comparisons between liquid output in direct use and effective liquid output in direct use through the tube or tent at similar operating conditions in Table I. In confirmation, little water collection was noted in the apparatus, even during long runs. This means that the number of large particles produced by these nebulizers and baffled out in the apparatus did not exceed the ability of the apparatus to evaporate liquid collected on the surface at these room temperatures.

As shown by Tables I and II, warming of the mist stream in the apparatus ranged from 1-10° C in the tubing depending on flow rate and mist-room temperature difference. Warming in the mask was evidently about 4.5° C and the mist was warmed to within 1 2° of room temperature in the tent. This, together with the associated data on fall in liquid humidity, indicates the degree of conversion of liquid to vapor humidity that can be expected in practice.

The liquid humidities sampled from the tent are low even for nebulizer type (E), which covered the floor with water, as are values obtained from the literature. Apparently, as pointed out by Arnold and Tovell,[11] it is difficult to maintain high liquid humidity in an enclosure.

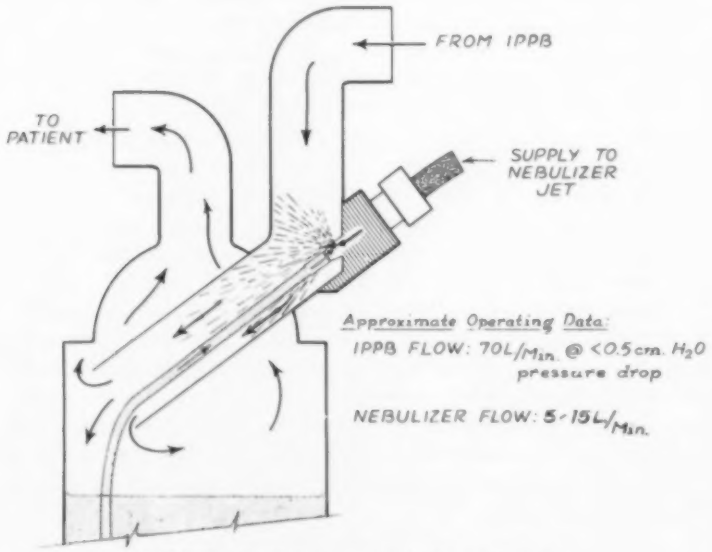

FIGURE 2: Mainstream nebulizer operation.

As shown by the data for nebulizers type (A) and (B) (Table I), liquid humidity production falls at high flow rates. However, liquid humidity was still produced by nebulizer type (A) at a dry gas flow rate of 85 L/min.

The effect of pre-existing humidity in the air stream to the nebulizer is shown most strikingly by the test of recirculation within an enclosure (Nebulizer type (A), Tables I and II). Operating temperature rose from a usual 15° C to 22° C and total humidity rose 10 per cent B.H. above any previous value for this nebulizer. Recirculation, by taking advantage of heating from the room and patient, produces the highest possible humidity from an unheated nebulizer. Room air admixing, although the data are obscured by high flow rate, also shows a rise in operating temperature.

When warming of mist in the airways was simulated by directing mist from nebulizer type (G) through one nostril and measuring as it emerged from the other (Tables I and II), liquid humidity dropped from about 30 per cent to about 10 per cent B.H. Whether this was because of baffling or warming is not known. At any rate, the amount of pure water liquid humidity reaching the lower airways may be much less than that delivered to the patient.

Nebulizer type (E) deserves special comment. It produced liquid humidities well above that of the other types, even when its output was passed through the baffle system of nebulizer type (A). It seems an excellent choice for side stream nebulization of IPPB assistors (see next section) if kept full and operated at maximum flow rate. The high humidity produced was partially dependent on this "over loaded" operation. Under other conditions it was not much more effective than other nebulizers; for instance, its normal flow rate was less and its effective humidity dropped sharply in mask or tent. The performance of this nebulizer is particularly significant because it indicates that nebulizers can be built to produce very high liquid humidity.

All of the above results concern the nebulization of pure water. However, a few comparisons of water and detergent solution* nebulization under identical operating conditions showed no significant difference in amount of liquid leaving the nebulizers.

The clinically important conclusions of the observations in light of previous information are:

1. Oxygen bubblers, especially if heated, and suitable air conditioning equipment[9] should provide near the 70 per cent relative humidity which is sufficient to prevent subjective symptoms in patients with normal airways and breathing patterns.

2. Cold nebulization provides the level of humidity necessary to prevent drying of the tracheo-bronchial tree except under the most adverse conditions. However, much of its clinical effect must be due to medication rather than humidification.

*Alevaire.®

3. Significantly higher humidities are obtained when a cold nebulizer is used to recirculate air in an enclosure than by other methods of cold nebulization.

4. To assure significant deposition of pure water in the lower airways, or to provide near 100 per cent body humidity for tracheostomy breathing, the operating temperature of most nebulizers must be raised by some form of heating.

Humidification for IPPB

IPPB assistance with completely dry gas has maximum drying effect because of a combination of factors. Administration is often through the mouth or tracheostomy, large tidal volumes and hyperventilation are common, and the usual subject is susceptible to drying because of pulmonary disease or serious illness. Without any humidification, significant drying may result even from short periods of IPPB assistance, for instance if the patient does not wet his mouth.

Humidification by the usual small side-stream nebulizer is sufficient to prevent drying during intermittent use of IPPB, especially if medication to thin secretions is included. On the average, such nebulization may provide 10 L/min. of nebulizer gas at 50 to 75 per cent B.H. which, when mixed with dry gas flowing at a mean rate of 40 L/min. during inspiration,[13] produces a mixture of 50 L/min. at 12 to 20 per cent B.H.; effective humidity is raised above these values by the amount of completely nebulized gas which collects in connecting tubing during expiration. The result is gas which approximates ordinary room air temperature and humidity. Under other circumstances, however, negligible humidity may be produced. Patients frequently inspire at mean rates of 70 to 80 L/min. with peak instantaneous flow rates up to 100 L/min.[13] Also, nebulizers may be slightly defective, and the nebulizer pressure tubing may not permit high nebulized gas flow rates. This may result, for example, in 5 L/min. of 50 per cent B.H. being mixed with 75 L/min. of dry gas to give only 3 per cent B.H.

When IPPB is used continuously, side stream nebulization is inadequate. Patients requiring such treatment cannot usually tolerate drying, and even slight drying effect may become significant if continued long enough. The small nebulizers quickly run dry and frequently plug, while continuous duty nebulizers produce somewhat lower humidity. The humidification provided by side stream nebulization is obviously inadequate for use with tracheostomy.

Adequate humidity for continuous IPPB assistance can be assured if the entire output of dry gas from the assistor passes through the contacting chamber of a nebulizer (*mainstream nebulization*). This is conveniently accomplished by connecting the room air admixing port of a suitable continuous duty nebulizer to the outlet connection of the IPPB assistor.* Operation of such a device is illustrated in Fig. 2. A spray

*Available through: Mist-O_2-Gen Equipment Company, Oakland, California.

of liquid is produced by a jet of high pressure gas in the usual manner, the entire flow from the assistor is mixed with this spray in the contacting chamber, and the resulting combined stream is then baffled and passed to the patient in the usual manner. The entire output is completely nebulized even at high flow rates, as shown by the data (Neb. A, Table I) on a nebulizer used for mainstream nebulization, and the observation that a visible mist is delivered to the patient. Heating the nebulizer provides any humidity desired, and this is easily accomplished by setting the nebulizer in a pan of water heated on a hot plate.[14]

The resistance added to the circuit is small, amounting to less than 0.5 mm. Hg. pressure drop at high flow rates, partly because of the aspirating effect of the jet. This effect, amounting to a negative pressure of 1-2 mm. Hg. at the assistor during expiration, has only a slight effect on operation of the pressure sensitive patient demand valves of some types of assistors.

Such devices have been in general use on our wards for over a year. They have made possible the routine use of IPPB assistors as respirators on the polio ward and elsewhere. In general, the nebulizer is used unheated for continuous naso-oral administration and is heated to near body temperature for tracheal administration or when dried out secretions are present.

More adequate humidity can also be obtained in the usual side arm nebulization method by adding a larger volume, say about 1 liter, to the tubing between the assistor and the exhalation valve. This is filled with nebulized gas during expiration. A continuous duty nebulizer is desirable, and it can be heated if necessary to obtain higher humidity.

SUMMARY

Available information plus knowledge of the physical processes involved in respiratory air conditioning provide a rational basis for the use of therapeutic humidification. Definite indications for humidification of dry air include gross drying of the upper airways, respiration by tracheostomy, and the presence of thick tracheo-bronchial exudate or decreased ability to move exudate and secretions through the trachea. Medication may be important in the treatment of airway drying, but its effects should not be confused with that of humidification.

With one exception, the nebulizers tested were found to produce total humidities of 30 to 60 per cent B.H.; this seems sufficient for most therapeutic needs. If near body humidity is required, nebulizers must be heated. Some of the variables concerned with final liquid humidity delivery in nebulization are: design, gas flow rate, apparatus used for delivery, and the patients' airways.

The usual side stream nebulization technique is not adequate in continuous IPPB assistance. A mainstream nebulization technique which provides adequate humidity is described.

The convenient absolute humidity expression "per cent body humidity" is proposed for use in respiratory physiology.

Extension of experimental work and further application of evaporative process principles to respiratory air conditioning in disease states are indicated to confirm and amplify the conclusions of this study. Further knowledge of the humidity provided in various inhalation therapy situations would be desirable.

RESUMEN

La información obtenible además del conocimiento de los procesos fisiológicos que existen en el aire respiratorio, dan una base racional para el uso de la humidificación terapéutica. Las indicaciones definidas de la humidificación incluyen: gran sequedad de las vías respiratorias superiores, respiración por traqueostomía y la presencia de exudado traqueobronquial o la capacidad deficiente para expulsar las secreciones por la tráquea. La medicación puede ser importante en el tratamiento de sequedad de las vías respiratorias pero no deben confudirse sus fectos con la humidificación.

Con excepción de uno, los nebulizadores probados produjeron humedades totales de 30 a 60 por ciento B.H.; esto parece suficiente para la mayoría de las necesidades terapéuticas. Si se requieren humedades como las corporales los nebulizadores deben calentarse. Algunas de las variantes relativas al rendimiento de humedad en la nebulización son: construcción, velocidad de paso, aparatos usados para proporcionar el paso y las condiciones de las vías respiratorias.

La nebulización por corriente lateral no es adecuada para la atención por el aparato de IPPB. Se describe una nebulización por medio de la corriente principal.

La expresión de humedad absoluta "por ciento de humedad" se propone para usarse en fisiología respiratoria.

Están indicadas, para confirmar y ampliar las conclusiones de este estudio la extensión del estudio experimental y la ulterior aplicación de los principios de los procesos de la evaporación al acondicionamiento del aire respiratorio.

Es de desearse mayor conocimiento de la humedad que se proporciona en varias circunstancias de inhalación.

RESUME

Une documentation valable ainsi que la connaissance des processus physiques que comportent les conditions de l'air respiratoire constituent une base logique pour utiliser l'humidification thérapeutique. Les indications précises pour l'humidification de l'air sont l'asséchement important des voies respiratoires supérieures, la respiration par trachéostomie, et la présence d'exsudats trachéo-bronchiques épais, ou la diminution de la possibilité de rejeter les exsudats et sécrétions par la trachée. Les médications peuvent avoir une action importante dans le traitement de l'asséchement des voies respiratoires mais ses effets ne doivent pas être confondus avec ceux de l'humidification.

Sauf une exception, il s'avéra que les nébulisateurs étudiés produisaient

des humidités totales de 30 à 60% de l'humidité du corps humain, ce qui semble suffisant pour la plupart des nécessités thérapeutiques. S'il faut obtenir une humidité voisine de celle nécessaire au corps humain, les nébulisateurs doivent être chauffés. Quelques-uns des éléments qui conditionnent la variabilité du degré final de l'humidité projetée par le nébulisateur sont: le modèle, le taux du débit du gaz, l'appareil utilisé pour la production, et les voies respiratoires du malade.

La technique habituelle de nébulisation avec production de vapeur n'est pas adaptée à un traitement continu.

Une technique de nébulisation susceptible de produire une humidité convenable est décrite.

L'emploi de l'expression d'humidité absolue "en pourcentage d'humidité humaine" est proposée pour la physiologie respiratoire.

Un complément du travail expérimental et une application ultérieure des principes du processus d'évaporation appliqué à la climatisation de l'air respiratoire dans les états pathologiques sont indiqués pour confirmer et amplifier les conclusions de cette étude. Il serait désirable de connaitre par des études ultérieures l'humidité fournie dans différentes situations de la thérapeutique inhalatoire.

ZUSAMMENFASSUNG

Brauchbare Information und Kenntnis der physigalischen Vorgänge, die bei der respiratorischen Klimatisierung beteiligt sind, bieten Gewähr für eine rationale Basis bei der Anwendung der therapeutischen Feuchtigkeitsregulierung. Absolute Indikationen für die Feuchtigkeitsregulierung eines trockenen Luftraumes umfassen starke Austrocknung der oberen Luftwegen, Atmung durch Tracheotomie und das Vorliegen von zähem tracheo-bronchialem Exsudat oder vermindertes Vermögen, Exsudat und Sekret durch die Trachea zu bewegen. Interne Behandlung kann wichtig sein in der Therapie der trockenen Luftwege, aber ihre Wirkungen darf man nicht verwechseln mit denjenigen der Feuchtigkeitsregulierung.

Es ergab sich mit einer Ausnahme, dass die geprüften Vernebelungsgeräte imstande waren, totale Feuchtigkeitswerte von 30-60% Körperfeuchtigkeit zu erzeugen; dies erscheint ausreichend für die meisten therapeutischen Bedürfnisse. Wenn der Körperfeuchtigkeit näher liegende Werte verlangt werden müssen die Vernebelungsgeräte erhitzt werden. Einige der veränderlichen Grössen, die mit der endgültigen Lieferung von flüssiger Luftfeuchtigkeit bei der Vernebelung zusammenhängen sind: Bauart, Ausmass der Gasströmung, für die Abgabe benutzte Aparatur und die Luftwege des Kranken.

Die gewöhnliche Technik der Seitenstromvernebelung ist nicht geeignet zur fortlaufenden IPPB—Assistenz. Beschreibung einer Vernebelungstechnik im Hauptstrom, die Gewähr bietet für eine adequate Feuchtigkeitsabgabe. Die geeignete Bezeishnung der absoluten Feuchtigkeit in "Prozent Körperfeuchtigkeit" wird zur Verwendung für die Physiologie der Respirationsorgane vorgeschlagen.

Ausdehnung der experimentellen Arbeit und weitergehende Anwendung der Grundsätze dr Verdampfungsprozesse auf die Klimatisierung bei der Atmung bei Krankheiten sind angezeigt. zur Bestätigung und Erweiterung der Schlussfolgerung dieser Untersuchung. Weitere Kenntnis der Feuchtigkeitsgrade, die bei verschiednartiger Situation von Inhalationstherapie verordnet werden, wäre wünschenswert.

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Temporary Collapse in the Treatment of Pulmonary Tuberculosis*

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The past decade marked the beginning of the era of chemotherapy of tuberculosis and more progress in the treatment of this disease was made than in all the years prior to 1946 when streptomycin was first introduced. Other anti-tuberculosis drugs of proved value such as Isoniazid (INH), Para-aminosalicylic Acid (PAS), Viomycin (VM), Pyrazinamide (PZA) and Cycloserine (CS) came into the armamentarium of phthisiologists and were initially used alone and later in combinations. It should be noted that coincidentally, advances in anesthesiology and surgery of the lungs were accomplished. Chemotherapy and resectional surgery in the therapy of tuberculosis were born and apparently are here to stay.

In the meantime, the old standby and friend, temporary collapse, suffered in its use and seems doomed to extinction. There are those who still advocate the use of artificial pneumothorax, pneumoperitoneum and phrenemphraxia. In a recent tour in Europe, I noted the widespread popularity of these procedures in Germany, France and England. This is reflected in their current literature which contains frequent reports on results of pneumotherapy; in contrast, only occasional reports appear in American literature. Scadding[1] of Brompton Hospital, London, in his recent Lettsomian Lectures emphasized the important place of artificial pneumothorax, phrenic paralysis and pneumoperitoneum with and without anti-bacterial treatment. Ellman, et al.,[2] report that even without chemotherapy, good results may be anticipated from artificial pneumothorax, provided cases are carefully selected.

In this paper, it is my purpose to report the changing concept and status of temporary collapse in the past 10 years at Fitzsimons Army Hospital and my own view based on experence since 1933.

Rest is generally accepted as fundamental in the treatment of pulmonary tuberculosis. Tuberculosis sanatoria were established in all countries in the world to provide a haven of rest for those afflicted with the disease as well as to segregate them from the general population. It may be mentioned that the concept of rest[3] is at present being challenged as to its necessity. Temporary collapse measures, namely, artificial pneumothorax, pneumoperitoneum, phrenic nerve paralysis and combinations of pneumoperitoneum and phrenemphraxia, basically are attempts to secure rest by so-called "splint" or "selective collapse" of diseased lungs. This is the *raison d'etre* of collapse therapy.

Artificial Pneumothorax

In 1888 Carlo Forlanini first introduced pneumothorax in the treatment of pulmonary tuberculosis. Since then, the procedure gained in-

*From the Pulmonary Disease Service, Fitzsimons Army Hospital.

creasing use until recent years. It took about 30 years for others to follow and in the United States and Asiatic countries, the peak of its popularity occurred in the 30's and 40's. This was only to be expected as the procedure was not only theoretically attractive but also provided the first effective weapon besides bed rest to be placed in the hands of the phthisiologist. Here, at long last, was something real, tangible and concrete that medical men could offer the afflicted, a sort of positive hope for the hopeless. In the early years it was employed only in unilateral cases which did not respond fast enough after three to six months of bed rest. It did not take long before therapeutic pneumothorax was used in practically all cases of pulmonary tuberculosis regardless of extent of disease—minimal, moderately advanced or even far advanced. Later, bilateral pneumothorax also came into use.

In retrospect, I shudder to think of not only the misuse but the abuse of this procedure. Practically every medical man learned how to induce pneumothorax. How many of us used to delight in the early conversion of some cases with positive sputa to negative, thus sending patients away from the sanatorium much sooner than mere bed rest permitted us in the past. Specifically, did we enjoy seeing "bread-winners" return to their work and thus become useful individuals again. All the patient had to do was to return for refills each week, twice a month or even once a month. Of course the vast majority of these patients had to be re-hospitalized because of relapse, contralateral spreads and/or reactivation of the disease, empyema, etc., and in the end—death. The few who did not relapse had to be "refilled" for years (my longest was 12 years) for nobody knew when to stop. In many cases the pneumothorax was discontinued because there was not available a needle long enough to reach the pleural space. At the annual meeting, American College of Chest Physicians in San Francisco in 1954, at a panel discussion on pneumothorax, the consensus of opinion was that the best type of pneumothorax should be terminated after two years. In this same meeting, I expressed the opinion that pneumothorax as a weapon against pulmonary tuberculosis was and always will be a poor one and therefore should be forgotten. *There no longer exists any indication for its use because the lesions which in the past have responded so well to pneumothorax are also the very type which respond so remarkably well with chemotherapy.*

In 1951, Mitchell[4] published six reports wherein he analyzed 557 cases of pneumothorax successfully induced over a decade (1930-1939) at Trudeau Sanatorium. He recommended the following rules in the management of pneumothorax:

1. Free anatomic collapse should be achieved or the pneumothorax abandoned.

2. Sudden persistent contraction and airlessness of a lobe or lung soon after induction is strong indication for abandonment of pneumothorax and consideration of some other type of procedure.

3. If cavity closure and sputum conversion do not occur within 3 to 4

months, abandonment and alternative forms of treatment should be seriously considered.

4. Abandonment of pneumothorax should be seriously considered if fluid sufficient to hide the hemidiaphragam continues to form a month or longer. Abandonment and prompt obliteration of the pneumothorax space is strongly indicated at the first sign of cloudy, purulent fluid or bacteriological evidence that the fluid is secondarily infected.

I personally endorse the above rules of management. However, I would like to point out that it would be difficult to find 10 out of 100 induced pneumothoraces which would not be abandoned after six to eight months if we were to follow the rules as suggested by Mitchell. So why should anybody start a pneumothorax at all and take the risk of complications? Some of the common complications of pneumothorax are:

1. Adhesions—50 to 75 per cent of all induced pneumothoraces will have varying degrees of pleural adhesions. A small percentage may be amenable to intrapleural pneumonolysis.

2. Effusion—pleural fluid will develop in a few days to six months in 70 to 80 per cent of all cases. Empyema will result in the majority of these cases.

3. Tension cavities—a not too infrequent occurrence.

4. Spread of disease—on the same and/or contralateral side.

5. Atelectasis of a lobe or more.

6. Fibrothorax and/or non-expandable lung.

7. Mediastinal hernia.

8. Air embolism—which may be severe enough to be fatal.

9. Subcutaneous ephysema—escape of air into the subcutaneous space may be so severe as to involve the chest, neck and face or may extend down to abdomen and lower extremities.

TABLE I

	PNEUMOTHORAX		PNEUMOPERITONEUM		PHRENEMPHRAXIA
Year	Initial	Refills	Initial	Refills	
1946	564	22,484	0	0	210
1947	264	11,784	123	4,493	114
1948	294	4,548	132	3,190	60
1949	150	3,368	319	6,319	37
1950	317	2,491	640	12,529	36
1951	34	1,067	660	14,350	46
1952	4	334	572	18,793	15
1953	0	32	98	5,501	0
1954	0	0	0	0	0
1955	0	0	0	0	0

The pneumoperitoneums initiated in 1954 and 1955 were performed only as space filling procedures following lower lobe resections.

10. Perforation of blood vessels—resulting in hemorrhage into pleural cavity.

11. Perforation of the lung—usually on initiation of pneumothorax and may also occur anytime during refills.

At Fitzsimons Army Hospital, therefore, therapeutic pneumothorax was completely abandoned in 1953 as a definitive procedure in the management of pulmonary tuberculosis (Table I).

Pneumoperitoneum

Pneumoperitoneum was introduced by Banyai in 1931. The partial collapse of the lung so obtained seems to exert beneficial effect on pulmonary tuberculosis similar to that obtained in pneumothorax. The popularity of pneumoperitoneum increased in the decade preceding the era of chemotherapy and recently, according to Trimble,[5] has largely replaced pneumothorax. For many years it was principally used in cases of bilateral tuberculosis and of unilateral lower lobe tuberculosis. Later, even unilateral upper lobe disease was treated with pneumoperitoneum coupled with phrenic nerve paralysis on the same side as it was found that impairment of pulmonary function resulting from collapse of lungs by pneumoperitoneum was only minimal. The complications of pneumoperitoneum, although less than in pneumothorax, are still numerous. We quote the following from a report of Bobrowitz[6] as a good list of the complications of pneumoperitoneum:

A. Thoracic Complications:
   1. Mediastinal emphysema
   2. Pneumothorax
   3. Bronchial obstruction and atelectasis
   4. Marked pulmonary collapse

B. Complications Due to Administration of Air:
   1. Air embolism
   2. Subcutaneous emphysema
   3. Febrile response
   4. Pain

C. Abdominal Complications:
   1. Adhesions
   2. Peritoneal fluid
   3. Intestinal obstruction
   4. Gastrointestinal symptoms and anatomic changes
   5. Acute appendicitis
   6. Tuberculous peritonitis
   7. Non-tuberculous peritonitis
   8. Peritoneal insult or mechanical peritonitis

D. Complications of Abdominal Wall:
   1. Hernia

E. Vascular Pressure:
   1. Lower extremity edema

The indications of pneumoperitoneum are basically the same as that of pneumothorax; however, patient acceptance of it is rather inferior to that of pneumothorax. Therefore, the use of this procedure has, like that of pneumothorax, become less and less popular with the success obtained with chemotherapy and resectional surgery of residuals. I agree also with Livingstone[7] of England who last year stated that he has never used pneumoperitoneum without temporary phrenic paralysis, which, *per se*, limits its usefulness to selected unilateral cases. Furthermore, the duration of pneumoperitoneum therapy is rather prolonged—2 to 5 years. At Fitzsimons Army Hospital, pneumoperitoneum reached its peak in 1951 and 1952 only to be practically abandoned in 1954 (Table I), because of the more desirable results obtained by the use of chemotherapy and resection of serious residuals. At present I use pneumoperitoneum only in those rare and extreme cases in which residual lesions, after prolonged chemotherapy, cannot be excised because of serious impairment of pulmonary function that would result if extensive surgery were performed.

Phrenic Nerve Paralysis

Phrenic nerve paralysis in the treatment of pulmonary tuberculosis was first proposed by Stuertz in 1911 for severe unilateral tuberculosis of the lower lobe of the lung. Sauerbruch, however, first performed this operation in 1904 in animal experimentation and indicated that the rest and collapse of the lung induced by hemidiaphragmatic paralysis favored healing. This work was supported by Schepelmann in 1913 who stated that even apical tuberculosis was benefited by this operation.

The popularity of phrenic nerve operations has varied since these procedures were first introduced. Although its use initially was limited mainly to treatment of lower lobe disease and as a supplement to bed rest in the treatment of minimal apical disease, these procedures have been further limited in their application by the advent of chemotherapy which in most cases has eradicated its use in the treatment of minimal disease. The operations first introduced were of a permanent collapse type (phrenic exeresis or phrenicectomy), but temporary paralysis of the hemidiaphragm (phrenemphraxis) is now generally preferred. Supplementary to pneumoperitoneum, its specific purpose is simply to increase the rise of the

TABLE II

Year	Pts. Treated to Inactive Stage	Pts. Treated with Chemo. Rx Alone in Per Cent	Pts. Treated with Chemo. and Temp. Collapse in Per Cent	Pts. Treated with Chemo. & Surgery in Per Cent	Pts. Treated with Rest Alone in Per Cent
1952	431	22.8	53.6	22.5	1.1
1953	527	42.0	28.0	30.0	0.0
1954	469	57.2	0.0	42.8	0.0
1955	397	51.9	0.0	48.1	0.0

Note: The decrease of patients in 1955 was due to reduction of beds for tuberculosis.

diaphragm. It often finds its field of usefulness here, especially in lower lobe involvement or in instances where the elevation of the diaphragm is limited after pneumoperitoneum has been induced.

The complications and failures of phrenic nerve paralysis consist of:

1. Operative complications: Damage to other nerves (vagus, sympathetic, etc.), vascular structures and thoracic duct may result during the operation. These are rare and then usually the result of having an inexperienced operator, or may be due to disturbed relationships which usually are noted in re-crush operations.

2. Secondary symptoms: Gastric distress, dyspnea, cardiac palpitation, etc., may follow a high rise of the diaphragm, particularly on the left side.

3. Failures of the diaphragm to rise after operation:

a. The presence of anamolous branches or positions of the phrenic nerve, which make it difficult to find and completely crush all branches of the nerve.

b. The diaphragm may not rise if the lung is bound down by pleural adhesions such as may be present following pleural effusion (this can be avoided if the patient is fluoroscoped to observe movement of the diaphragm prior to recommending the procedure).

c. The tone of abdominal muscles may be a factor. Lax muscles do not support a continuous intra-abdominal pressure necessary to elevate the diaphragm.

4. Permanent paralysis of the hemidiaphragm may occur following phrenemphraxis. Reports on the incidence of this vary from 6 to 20 per cent. As a result of permanent paralysis of the hemidiaphragm, I have seen in postmortem examinations, atrophied muscle almost as thin as ordinary paper. It is therefore quite obvious that in crushing the nerve, care should be exercised so that permanent injury to the nerve does not result. This is, however, easier said than done, as there is no instrument which gauges the amount of pressure necessary to crush the nerve. This is determined solely on the previous experience of the surgeon.

As a primary definitive procedure, phrenic nerve operations were comparatively seldom used at Fitzsimons Army Hospital (Table I). The majority of the 518 cases of phrenic nerve paralysis since 1946 were performed as adjuncts to pneumoperitoneum to obtain further rise of the diaphragm. My own experience with phrenemphraxia exceeds the total number done at this hospital in the past decade. I shall never forget the years when residents in a sanatorium wagered on who could excise the longest piece of phrenic nerve. Those were the days of phrenic exeresis or phrenicectomy. Aside from the resulting severely atrophied hemidiaphragm to almost parchment paper thinness, a far worse complication is the development of paradoxical respiration which usually follows when collapse procedures such as thoracoplasty are performed on the contralateral side. It is therefore not surprising that operations on the phrenic nerve were dropped at Fitzsimons Army Hospital in 1953.

Discussion

The experience at Fitzsimons Army Hospital in the overall management of pulmonary tuberculosis points to the importance of chemotherapy and surgical excision of residuals as the principal weapons employed to combat the disease. After adequate use of anti-tuberculosis drugs in combinations such as SM-PAS, SM-INH, SM-INH-PAS, INH-PAS, SM-VM, etc., usually after six to eight months, rarely longer, residuals of pulmonary lesions revealed by ordinary postero-anterior roentgenograms, laminograms and/or bronchograms, are excised. The amount of diseased lung removed is usually governed by the extent of the residuals and pulmonary reserve the patient has as shown by external and internal pulmonary function tests. The above, in brief, is the master plan of treatment of pulmonary tuberculosis at Fitzsimons Army Hospital in the past two years. In Table II are the statistics derived from patients treated to the inactive stage at this chest center since 1952. Unfortunately, our research files do not go farther back than 1952. It is most interesting to note that only 1.1 per cent of 431 patients who became well in 1952 were managed with bed rest alone. Since then all patients received chemotherapy in addition to rest. Furthermore, it is striking to see that in 1952, 53.6 per cent of the patients were managed by chemotherapy and temporary collapse; this figure dropped to 28 per cent in 1952 and to nothing in the past two years. Note also that the number of patients who were treated with chemotherapy alone and with drugs plus surgery in 1952 increased roughly by 250 per cent.

We would like to point out that the discovery of pulmonary tuberculosis in military personnel is probably much earlier than in most civilian populations. The availability of previous chest films from induction centers and routine roentgenograms from outlying military installations, as well as previous medical records, are distinct advantages in the final decision of therapy of each individual patient. Therefore, in the great majority of our patients, we are able to determine the duration of the disease process. Early discovery and the relatively short morbidity of pulmonary tuberculosis enable us to attain the many "cures" in our hospital by the use of chemotherapy alone and/or surgical excision. Temporary collapse procedures have not been used in the overall planning of therapy of pulmonary tuberculosis in the past three years at Fitzsimons Army Hospital.

SUMMARY AND CONCLUSIONS

1. The use of temporary collapse procedures—artificial pneumothorax, pneumoperitoneum and phrenic nerve operations was reviewed.

2. Artificial pneumothorax and phrenic nerve paralysis are considered obsolete procedures.

3. Reversible collapse procedures—pneumotherapy and phrenic nerve paralysis, are no longer considered as primary and/or definitive procedures.

4. If, after the adequate use of anti-tuberculosis drugs, cavitary lesions are caseo-nodose residuals which are potentially dangerous to relapse remain, surgical excision is the procedure of choice.

5. Pneumoperitoneum may be used only as a last resort in far advanced cases when, after adequate and prolonged chemotherapy, surgical excision of cavities and/or serious residuals cannot be performed because of serious impairment of pulmonary function. In those rare patients in whom chemotherapy cannot be used because of severe toxicity, pneumoperitoneum may be considered.

RESUMEN

1. Se revisa el uso de procedimientos de colapso temporal (neumotórax, neumoperitoneo y operaciones del frénico).

2. El neumotórax artificial y la parálisis del frénico se consideran procedimientos anticuados.

3. Los procedimientos de colapso reversible—neumoterapia y parálisis del frénico—no se consideran ya como procedimientos primarios o definitivos.

4. Si después del uso adecuado de las drogas antituberculosas las lesiones cavitarias son caseo-nodosas residuales que son potencialmente peligrosas por las recaídas, el procedimiento de elección es la excisión quirúrgica.

5. El neumoperitoneo puede usarse sólo como último recurso en casos extremadamente avanzados cuando, después de adecuada y prolongada quimioterapia no se puede hacer de las cavidades y hay contraindicación a la cirugía por insuficiencia respiratoria. En casos en que la quimiote rapia no puede usarse por severa toxicidad el neumoperitoneo podría considerarse.

RESUME

1. L'auteur passe en revue les procédés de collapsothérapie temporaire (pneumothorax artificiel, pneumopéritoine, interventions sur le nerf phrénique).

2. Il considère le pneumothorax artificiel et la paralysie phrénique comme des moyens périmés.

3. Les méthodes de collapsus réversible, pneumothorax et paralysie du nerf phrénique, ne sont plus considérées comme des moyens à utiliser d'emblée et à action indiscutable.

4. Si, après emploi correct des médications antituberculeuses, les lésions cavitaires constituent des résidus caséonodulaires qui sont un potentiel dangereux de rechute éventuelle, l'exérèse chirurgicale est le procédé de choix.

5. Le pneumopéritoine peut être utilisé en dernier ressort seulement, dans les cas très avancés, lorsque, après chimiothérapie correcte et prolongée, l'exérèse chirurgicale des cavités et des lésions résiduelles graves ne peut être pratiquée par suite de trouble grave de la fonction pulmonaire. Dans ces cas limites pour lesquels la chimiothérapie ne peut être utilisée à cause de réactions toxiques qu'elle provoque, le pneumopéritoine peut être pris en considération.

ZUSAMMENFASSUNG

1. Die Anwendung von temopären Kollapsmassnahmen künstlicher Pneumothorax, Pneumoperitoneum und Operationen am Nephren. wurden besprochen.

2. Der künstliche Pneumothorax und die Lähmung des Zwerchfellnerven werden als veraltete Massnahmen angesehen.

3. Reversible Kollapsmassnahmen—Pneumotheraphie und Lähmung des Zwerchfellnerven werden nicht mehr als primäre und/oder definitive Massnahmen angesehen.

4. Wenn nach dem adaequaten Gebrauch von antituberkulösen Medikamenten kavernöse Veränderungen zu käsig-knotigen Restzuständen werden, die eine potentielle Gefahr zum Rezidiv behalten, ist die chururgische Excision das Verfahren der Wahl.

5. Das Pneumoperitoneum lässt sich nur als letzte Möglichkeit bei weit fortgeschrittenen Fällen anwenden, sofern nach adaequater und langdauernder Chemotheraphie die chirurgische Entfernung von Kavernen und/oder erheblichen Restherden nicht erfolgen kann wegen erheblicher Schädigung der Lungenfunktion. In solchen Fällen, in denen die Chemoteraphie nicht zum Einsatz kommen kann infolge schwerer Toxizität, kann das Pneumoperitoneum in Erwägung gezogen werden.

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SECTION ON CARDIOVASCULAR DISEASES

The Application of Hypothermia in the Correction of Cardiovascular Lesions: A Study of 140 Cases

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The concept of lowering body temperature as an adjunct to surgical therapy is not new. In a minor way, it has been frequently used to produce temporary tissue insensitivity for incision and drainage of abscesses. It has also been applied to decrease toxicity in patients with non-viable extremities who could not tolerate the insult of a major surgical amputation. Despite these uses, its value has been at best, insignificant. Recently, however, with the great impetus created by the successful correction of previously hopeless cardiovascular lesions, the potential value of hypothermia has been reassessed. Its ability to decrease metabolism and thereby permit extended periods of circulatory arrest represented a potential approach to surgery within the cardiac chambers. Much work, both experimental and clinical, has been accomplished during the last several years. From this, hypothermia emerged as a useful tool with application in surgery both inside and outside the heart. This report will present our approach to the problem of hypothermia as to first, effects; second, technic and third, clinical application.

Effects of Hypothermia

Though hypothermia can extend over a considerable range of temperature variation, this presentation will be concerned with experimental and clinical observations, made during total body cooling from 37 to 24 degrees centigrade. It is well documented that the fundamental effect of hypothermia is reduction of the rate of metabolism in all body systems. This rate of metabolic slowing is almost linear to approximately 24 degrees centigrade where response is less than 50 per cent of normal. Associated with this change are other physiologic alterations which are equally important. Among these might be mentioned the decrease in heart rate, stroke volume and cardiac output which result in systemic hypotension and are accompanied by a generalized vasoconstriction. There is a rise in blood oxygen saturation which probably reflects decreased utilization and dissociation. The respiratory rate falls and may eventually cease. If not

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adequately supported, this can result in severe metabolic derangements. A progressive neurogenic depression is also observed and may be responsible for some of the serious cardiac irregularities encountered in deep hypothermia.

In addition to these effects of hypothermia, many of which are of value in various surgical situations, there are also several inherent and ever present dangers. They are: first, the onset of significant cardiac rhythm disturbances and second, the development of postoperative hemorrhagic tendencies.

We have observed various types of cardiac irregularities. The occasional incidence of supraventricular tachycardia or wandering pacemaker cannot be attributed to cooling per se since they are just as likely to occur in the normothermic individual undergoing cardiac surgery. On the other hand, atrial fibrillation and, the more serious, ventricular fibrillations are definitely associated with the cooling process. Though some observers have reported atrial fibrillations in approximately 50 per cent of patients, our incidence has been insignificant and only noted in patients carried below 26 degrees centigrade. These, however, will revert to a normal sinus rhythm on rewarming.

Ventricular fibrillation, though a constant concern, has occurred in only seven of 140 or an incidence of 5 per cent. In two it developed during anesthesia induction. The remaining five were secondary to manual or instrumental manipulation of the heart. Its cause has been variously ascribed to a lowering of the myocardial threshold due to cold itself, a sudden change in blood pH, either acidosis or alkalosis, a reduction of serum potassium level or a neurogenic depression and imbalance. Regardless of etiology, we have found that slow cooling combined with hyperventilation and gentle cardiac manipulation have kept the incidence at a minimal level. In our hands, conversion of a fibrillation occurring during induction in a patient with a large left to right shunt has been a hopeless task despite all types of heroic measures. In all other instances, it has been possible to reconvert the heart by a combination of manual cardiac compression and electrical shock. No type of drug therapy has been employed. Occasionally a patient in deep hypothermia may have to be rewarmed to 26 degrees centigrade for conversion. However, this can be rapidly accomplished by constant flushing of the thoracic cavity with warm saline solution.

The second danger of hypothermia, the development of postoperative bleeding tendencies, in our experience has represented more of a potential than actual hazard. In the experimental animal, platelets are consistently reduced in significant numbers but we have never been able to adequately substantiate this in man. In our opinion, the most important deterrent to postoperative hemorrhage is to delay closure of the wound until the patient is sufficiently rewarmed to return the blood pressure to relatively normal limits. Three of our patients have had significant bleeding; an incidence of 2.1 per cent. Two were successfully managed by thoracentesis. One required re-exploration at which time numerous blood clots were removed but no active bleeding was encountered.

From this brief discussion of the major effects of hypothermia, its potential clinical application in various cardiovascular and other surgical procedures can be appreciated. If carefully administered and cognizant of the complications, with regard to their prevention and treatment, its value will far outweigh its inherent dangers. This is particularly true when total body cooling is used in closed cardiac procedures or in non-cardiac operations in general.

Technic

The technic employed in hypothermia is not difficult. Preoperative medications are the same in type and dose as those prescribed in the normothermic individual. Following induction, a constant recording esophageal or rectal thermocouple is inserted. A femoral artery is catheterized and the aortic pressure measured through a strain gauge. The electrocardiogram and electro-encephalogram are continuously recorded. For the information of the surgeon, the pressure-pulse contour and the electrocardiogram are always visible on a monitoring oscilloscope.

The actual cooling process is not started until the patient is in third stage anesthesia. A refrigerating fluid is circulated through a special rubber mattress placed under the patient. This mattress can surround the trunk, arms and legs similar to a sleeping bag. Fluid containing tubes run to a temperature control unit and in this manner, it is possible to use the same equipment for both cooling and rewarming.

It is important that shivering be prevented. This is accomplished by maintaining sufficient depth of anesthesia or by administering small doses of curare when it is first noted. Shivering will not only counteract the effect of the refrigerant but will actually cause the temperature to rise. It also increases oxygen consumption which we believe has a detrimental effect on the hypothermia patient.

We have noted that our method of cooling is slower than other reported technics. To lower the temperature from 37 to 28 degrees centigrade may require from one to three hours depending on the size of the individual and the amount of left to right shunt present. Most rapid cooling occurs in the non-cardiac patient or in the cardiac patient with no shunting defect. Nevertheless, we prefer the slower method since it is felt to be in part responsible for our low incidence of ventricular fibrillation. In this same regard, we believe it is essential that the surgical team be on hand during induction and cooling to perform any emergency procedure indicated should a serious cardiac arrhythmia develop.

Cooling is discontinued when the patient's temperature is approximately two or three degrees above the desired level. This amount of additional fall can be anticipated. The mattress is then allowed to fall to the sides of the operating table so that as much or as little of the patient's body, necessary for the operative incision, can be exposed.

In those patients requiring open cardiac procedures, hyper-ventilation is carried out for five minutes prior to circulatory occlusion. This keeps the patient in a state of respiratory alkalosis and possibly lowers the incidence of ventricular fibrillation. During the period of circulatory arrest,

ventilation is discontinued and the lungs are allowed to collapse. With restoration of blood flow, rewarming is begun and, anesthesia wise, the patient can be carried on oxygen alone.

Wound closure is delayed until the recorded blood pressure is within normal limits. This is felt to be the most significant factor in preventing postoperative hemorrhage. The patient is not sent to the recovery room until spontaneous respiration is adequate and the body temperature is between 33 and 34 degrees centigrade.

Clinical Application of Hypothermia

During the last three years we have employed hypothermia in a variety of cardiovascular conditions. These can be divided into two categories; first, cardiovascular procedures performed without circulatory occlusion and second, direct vision cardiac operations performed under complete circulatory arrest. Our experience with 140 such cases would indicate that in certain instances the technic is of unquestioned value. In other cases, it has virtue but is not essential. Finally, in some anticipated procedures, in our opinion, it should not be employed at all (Table I).

Closed Cardiovascular Operations

One hundred twelve cardiovascular operations for a variety of conditions have been performed under hypothermia without circulatory occlusion. The outcome was fatal in eight instances; an overall mortality rate of 7.1 per cent. The corrected mortality rate was only 2.6 per cent since five of the patients died during the postoperative period of conditions unrelated to hypothermia. Thus all deaths occurring with hypothermia for closed cardiovascular procedures were due or related to the development of serious rhythm disturbances (Table II).

Three infants with the Tetrology of Fallot had Blalock-Taussig operations performed under hypothermia of 30 to 32 degrees centrigrade. The

TABLE I
RESULTS IN 140 PATIENTS

Procedure	Number of Cases	Ventricular Fibrillation		Deaths Associated With Hypothermia		Deaths Not Associated With Hypothermia		Total Deaths	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Closed Cardiovascular Operations	112	5	4.5	3	2.6	5	4.5	8	7.1
Open Heart Operations	28	2	7.1	3	10.7	1	3.5	4	14.7
TOTAL	140	7	5	6	4.3	6	4.3	12	8.5

prime consideration for its use was to improve oxygenation in these severely cyanotic patients. We were impressed that the resultant decreased metabolism and oxygen utilization did improve the patient's color. There was also a significant lowering of the heart rate which greatly facilitated dissection and establishment of the anastomosis. Since one of our main indications for surgery was a rapidly rising hematocrit with its potential hazard of secondary thrombosis, we felt the thrombocytopenic accompanying cooling would also be of theoretical benefit. Excellent results were obtained in each case. Most of our patients with this malformation are doing well and are awaiting the advent of a safe extracorporeal circuit which will permit intracardiac correction of the defects. For those who do require a shunting procedure, however, we believe hypothermia has definite virtue. This is especially true in the infant under two years of age where surgery at normothermic levels carries a considerable risk.

Two patients were operated upon with the erroneous diagnosis of val-

TABLE II
RESULTS IN 112 CLOSED CARDIOVASCULAR OPERATIONS WITHOUT CIRCULATORY OCCLUSION

Procedure	Number of Cases	Ventricular Fibrillation		Deaths Associated With Hypothermia		Deaths Not Associated With Hypothermia		Total Deaths	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Tetrology of Fallot	3	....	....	....	....	....	....	....	....
Infundibular Stenosis	2	2	100	....	....	....	....	....	....
Patent Ductus Arteriosus	36	2	5.5	2	5.5	....	....	2	5.5
Coarctation of Aorta	13	....	....	....	....	....	....	....	....
Aortic Aneurysms and Aortic Occlusive Disease	25	....	....	....	....	....	....	....	....
Sinus Valsalva Fistula	1	1	100	1	100	....	....	1	100
Transposition of Great Vessels	1	....	....	....	....	....	....	....	....
Portacaval Shunt	1	....	....	....	....	....	....	....	....
Intracranial Aneurysms	30	....	....	....	....	5	16.6	5	16.6
TOTAL	112	5	4.5	3	2.6	5	4.5	8	7.1

vular pulmonary stenosis. At thoracotomy the lesions were found to be infundibular. Both patients were carried at 31 degrees centigrade. Closed infundibulectomies were performed and in each instance ventricular fibrillation occurred while biting out sections of the obstructing myocardium. Manual cardiac compression supplemented by electrical shock restored a normal sinus rhythm and the patients made uneventful recoveries. We believe this complication was caused by the stimulation of trauma on a heart whose threshold was lowered by cooling. Our present policy in such cases is to perfuse the coronaries with neostigmine, occlude the inflow tracts and excise the obstructing myocardium through an open right ventriculotomy.[1] The body temperature is kept at 28 degrees centigrade to allow at least eight minutes of occlusion. Ultimately, however, hypothermia will undoubtedly be surplanted by the artificial circulation in this type of patient.

There were 36 patients with patent ductus arteriosus operated upon under hypothermia of 30 to 32 degrees centigrade. Cooling was used for two purposes, first to quiet a large, active and rapidly beating heart and second, to help sustain those patients who were considered poor surgical risks because of pulmonary hypertension. The results were gratifying. In the patients with severe tachycardia, the operative field was noticeably quiet and division and suture of the ductus greatly facilitated. Among the poor risk patients with pulmonary hypertension, two deaths occurred. Fatal fibrillation during induction developed in a three-year-old child with a large ductus, pulmonary hypertension and interatrial septal defect. A second child with a large ductus and left pulmonary artery hypoplasia began fibrillating during dissection of the lesion. Conversion was accomplished but an effective regular cardiac contraction could not be sustained. These results have made us shy away from hypothermia in other similar patients. Cooling is now limited to those who have tachycardia sufficient to cause myocardial strain or to interfere with the technical aspects of surgery.

Total body cooling has been employed in 13 of the last 40 coarctations of the aorta. The specific indications were first, coarctations in infants under two years of age; second, lesions associated with extensive aneurysmal dilatation of the aorta or intercostals and third, coarctations in patients with known myocardial damage. In infants where it is uncertain whether the collateral circulation is sufficient to allow prolonged occlusion of the aorta without subsequent renal or spinal cord damage, hypothermia of 30 to 32 degrees centigrade provides this desired safety factor in addition to quieting a usually overactive heart. It also appears to diminish the laryngeal edema occasionally seen after endotracheal intubation in infants. Massive aneurysmal dilatation of the aorta and collateral intercostals is frequently observed and may be so extensive that resection of the coarcted segment is not attempted. With hypothermia, dissection of these paper thin areas is aided because of the reduced head of pressure in the vessel. Similarly, hemorrhage following an inadvertent laceration is less extensive and more easily controlled. One patient operated upon had a coarctation

and a previous significant coronary occlusion and myocardial infarction. The rationale for the use of hypothermia was to decrease the heart rate, stroke volume and cardiac output and thereby relieve the acute insult to the myocardium caused by cross clamping the aorta. The 13 patients cooled for the stated reasons had the coarcted segments successfully removed with uneventful postoperative courses.

There were 26 patients with aortic aneurysms, both thoracic and abdominal, and aortic occlusive disease who were cooled to the same degree as just mentioned. Hypothermia proved of value in aiding the dissection, decreasing blood loss and permitting extended periods of aortic occlusion without neurologic damage. The thoracic aorta could be safely obstructed for one hour and the abdominal aorta for twice that time. Three of these patients developed extensive postoperative bleeding. Two responded to thoracentesis, however, the third required re-operation for evacuation of blood clots. With these exceptions the overall results were excellent and no other complication, which could be attributed to hypothermia, was encountered.

One patient with a large sinus of valsalva fistula was unsuccessfully treated. During attempted closure of the lesion, ventricular fibrillation occurred. This was converted and without further attempts at fistula closure, the patient was sent to the recovery ward. Six hours later the arrhythmia recurred and resulted in death. This complication was believed due to operative interference with the coronary circulation rather than the use of hypothermia. However, further knowledge of this lesion as regards its pathologic anatomy would indicate that hypothermia will not be adequate to permit its successful obliteration. The necessary surgical procedure would appear to depend upon the safe application of an extracorporeal circuit.

One patient with a transposition of the great vessels was operated upon under hypothermia of 30 degrees centigrade. The basis for its application was the same as that already presented for the cyanotic tetrology of Fallot. The infant was severely ill, cyanotic and had a hematocrit of 84. The procedure described by Baffes,[2] in which the inferior vena cava is transposed to drain into the left atrium and the right pulmonary vein is anastomosed to the right atrium, was employed. The result was most gratifying. There was marked lessening of the cyanosis and the hematocrit at the time of discharge had fallen to 57. A venous angiocardiogram through the femoral vein demonstrated adequate function of the operative repositioning of the cava and pulmonary vein. Until more complete and safe corrective operations are available, the Baffes procedure performed under hypothermia seems to greatly improve these unfortunate individuals.

Total body cooling also appeared to have application in the cirrhotic patient requiring a portacaval shunt. It was believed indicated when liver function was so depressed that surgery at normothermic levels was contraindicated. The cooling not only decreased the amount of anesthetic agent administered but, by lowering liver metabolism, lessened the possibility of postoperative hepatic failure.

One patient with chronic jaundice, recurrent hematemesis and liver failure had a direct end-to-side portacaval shunt established under hypothermia of 30 degrees centigrade. This individual would most certainly have gone into hepatic coma under normal operative conditions. Hypothermia provided the needed safety factor to carry the patient successfully through the significant anesthetic and operative insult imposed on an already severely damaged liver.

This technic has offered hope to additional patients who formerly were denied the possible advantages of the shunt operation. With further application it may even lower the postoperative morbidity in those patients with less severe hepatic changes.

The remaining 30 patients in the category of cardiovascular lesions repaired under hypothermia without circulatory occlusion had various types of intracranial aneurysms and vascular malformations. The application of total body cooling in these individuals was predicated upon its effect in decreasing cerebral edema both during and after operation and in allowing short periods of cerebrovascular occlusion. Clinically, it has proved efficient in the former. However, in the latter regard, periods of six to eight minutes of occlusion are insufficient to adequately perform the surgery required. New technics of hypothermia, at present being studied, should meet these expanded requirements.

TABLE III
RESULTS IN 28 OPEN HEART OPERATIONS WITH COMPLETE CIRCULATORY OCCLUSION

Procedure	Number of Cases	Ventricular Fibrillation		Deaths Associated With Hypothermia		Deaths Not Associated With Hypothermia		Total Deaths	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Pulmonary Valvular Stenosis	11	....	....	....	....	....	....	....	....
Interatrial Septal Defect	16	1	6.2	2	12.4	1	6.2	3	18.7
Secundum	12	....	....	....	....	....	....	....	....
Primum	2	....	....	....	....	1	50	1	50
Atrioventricularis Communis	2	1	50	2	100	....	....	2	100
Pulmonary Aortic Window	1	1	100	1	100	....	....	1	100
TOTAL	28	2	7.1	3	10.7	1	3.5	4	14.2

Open Cardiac Operations

The second major category of patients undergoing hypothermia were those on whom open cardiac operations were performed during complete circulatory interruption. These included pulmonary valvular stenosis, pulmonary aortic window and interatrial septal defect. The obvious indication for body cooling was to permit temporary cessation of blood flow and assure an accurate and complete repair of the defect by direct vision in an open and relatively dry heart. There were 28 patients treated with four deaths (14.2 per cent). Ventricular fibrillation developed in two patients (7.1 per cent). Both succumbed and are included in the deaths just mentioned. The arrhythmia had its onset during induction in one patient and during cardiac manipulation in the other (Table III). In contradistinction to the group of patients in whom the circulation was not occluded, where all deaths were related to arrhythmia, only half of the deaths in the open heart group could be attributed to this cause.

We believe the direct open attack on the stenotic pulmonary valve is superior to the closed valvulotomy and our last 11 patients were handled in this manner. Initially, hypothermia of 28 degrees centrigrade was used but experience has shown that this depth is not required. We have steadily decreased the amount of cooling to our present figure of 32 to 33 degrees centigrade. Since the open portion of the operation can be performed in less than three minutes, it is assumed the procedure could be safely done in a normothermic individual. Nevertheless, we have been reticent to relinquish the last several degrees of cooling because of the protection they provide should a situation be encountered that would take over three minutes to resolve.

There are several points of interest regarding surgical technic. To obtain a dry operative field, it is not necessary to occlude both inflow and outflow tracts. Obstruction of the cavae is sufficient. Air emboli in the unobstructed pulmonary artery has not presented a problem. This technic has been of particular benefit in the small infant where cross clamping the outflow tracts markedly constricts an already tiny operative field. It is important that the pulmonary artery be opened as close to the valve as possible and the commissures be incised to the annulus. Finally, a finger or large hemostat should be passed into the ventricle to be certain no associated infundibular stenosis is present.

There has been no morbidity or mortality connected with this procedure. The results have been excellent and postoperative catheterization has revealed right ventricular pressures to be normal or nearer normal than those obtained following closed valvulotomy.

One patient with a massive pulmonary aortic window was operated upon under hypothermia of 28 degrees centigrade. During division and suture of the lesion, ventricular fibrillation occurred. The total period of vascular stasis was 12 minutes. Manual cardiac compression was carried out for almost six hours and only discontinued when the heart failed to show evidence of electrical activity. This patient presented a lesion too extensive to be properly managed under hypothermia. An adequate recon-

struction of the great vessels could not be completed within the eight minute safe period. A small defect well out on the outflow tract could undoubtedly be successfully managed. However, since it is almost impossible to determine preoperatively the size of a window, especially with regard to its proximal extent and possible valve involvement, it would seem that repair should be attempted only if an extracorporeal circulation is available.

The final group of patients to be discussed are those with interatrial septal defect. Though many operative procedures have been devised to repair this lesion, our experience with the closed heart procedures, with the exception of atrioseptopexy, has been discouraging. Very small secondary defects are often impossible to locate with the blindly palpating finger and are therefore incompletely closed or missed entirely. Several external repairs performed on a greatly distended and wildly beating heart have torn through during surgery or in the early postoperative period. For these reasons, plus the belief that there is no substitute for direct vision, we have relied on hypothermia and an open heart to repair the last 16 defects.

The patient is cooled to approximately 28 to 30 degrees centigrade and the right atrium digitally explored. Both inflow and outflow occlusion are employed. Three things were particularly impressive at cardiotomy. First was the high incidence of secondary defects which could not be palpated. Second was the firm tissue which constituted the rim of the defect and gave substance to the suture closure. Third was the facility with which transposed veins could be repositioned into the left atrium. Fear of air embolism was considerable. However, this complication was usually avoided by allowing the left heart to fill by spillover from the right before the final suture in the defect was tied. Significant air was trapped in the coronaries in one patient. Approximately one hour of intermittent cardiac compression was required to establish an effective normal rhythm. The patient was comatose for five days but has subsequently made a complete recovery.

Three deaths occurred in the series giving an overall mortality rate of 18.6 per cent. However, this figure becomes less significant when one considers the type lesions involved. There were 12 patients with septum secundum defects; all successfully repaired without mortality. In two instances a septum primum defect was encountered. In one patient, the extent of the defect and the surrounding relationships were misinterpreted during suture. The condition was corrected but the delay was sufficient to produce irreversible myocardial damage. The second patient did well except for a temporary partial heart block postoperatively. Therefore the mortality rate with primum defects was 50 per cent. Surgery was also attempted on two patients with atrioventricularis communis lesions. One died of cardiac arrhythmia during induction. In the second patient, the defect including the deformed mitral valve was repaired but on restoring the circulation an effective cardiac contraction could never be established. The mortality rate was 100 per cent. From these figures it would appear

that hypothermia can be considered adequate for the successful correction of all secundum defects and possibly primum lesions. Repair of the common atrioventricular canal with its associated valvular deformities will require additional time which can best be obtained by employing a pump-oxygenator system.

SUMMARY

A study was made of 140 patients who were operated upon under hypothermia for cardiovascular lesions. One hundred twelve had the operations performed without occlusion of the circulatory system. Of eight operative deaths, only three could be directly related to the body cooling.

Open cardiac procedures were performed in 28 instances with complete circulatory arrest for periods varying from two to 10 minutes. Of four operative deaths three were associated with hypothermia.

RESUMEN

Se estudiaron 140 enfermos operados bajo hipotermia por lesiones cardiovasculares. 112 sufrieron sus operaciones sin oclusión del sistema circulatorio. De las ocho muertes operatorias, sólo tres podrían tener relación con el enfriamiento directamente.

Se realizaron 28 operaciones a corazón abierto con paro circulatorio variando de 2 a 10 minutos. De cuatro muertes operatorias, tres estuvieron asociadas a la hipotermia.

RESUME

L'auteur rapporte une étude de 140 malades opérés sous hypothermie pour des lésions cardiovasculaires. 112 subirent des interventions sans arrêt du système circulatoire. Sur les 8 morts opératoires, trois seulement peuvent être liées directement au refroidissement.

Des interventions à coeur ouvert furent pratiquées dans 28 cas avec arrêt complet de la circulation pendant des laps de temps allant de 2 à 10 minutes. Sur quatre morts opératoires, trois furent imputables à l'hypothermie.

ZUSAMMENFASSUNG

Es wurden 140 Patienten untersucht, die wegen cardiovasculärer Veränderungen unter Hypothermie operiert wurden. Bei 112 wurden die Eingriffe vorgenommen ohne Verschluss des Kreislaufes. Von 8 operativen Todesfällen konnten nur 3 in direkte Beziehung gesetzt werden zu der Unterkühlung des Körpers.

Eingriffe am offenen Herzen wurden in 28 Fällen vorgenommen mit vollständigem Kreislaufstillstand für Zeitabschnitte, die zwischen 2 und 10 Minuten lagen. Von 4 operativen Todesfällen standen 3 in Verbindung mit der Hypothermie.

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Atrial Septal Defect: An Evaluation of Surgical Closure*

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Successful surgical closure of an atrial septal defect was first performed by Bailey[1] in January, 1952, employing the method he terms atrio-septo-pexy. Cohn[2] in 1947 had reported results of the first experimental closure of defects in the atrial septum, and only a year later Murray[3] reported the first attempt at repair in a 12-year-old child by approximating the anterior and posterior atrial walls in the region of the septum. While early-post-operative evaluation of this case was optimistic, cardiac catheterization 14 months post-operatively by Keith and Forsyth[4] demonstrated a substantial left-to-right shunt and significant pulmonary hypertension with one episode of cardiac failure during this period.

Within two years of Bailey's first successful closure by atrio-septo-pexy, three other techniques of successful surgical correction of this relatively common congenital cardiac defect were reported in the literature. Sondergaard[5] in Denmark and Bjork and Crafoord[6] in Sweden introduced the method of circumclusion. Gross[7] applied a prosthesis of rubber or woven nylon to the right atrium and closed the defect through this "atrial well." Lewis[8] and Swan[9], employing hypothermia, were the first to work in an open heart under direct vision, although later Lillehei[10, 11] and Cooley and Kirklin[12] initiated the use of an extracorporeal circulation.

To evaluate the results of surgical closure of the various types of atrial septal defect by the several techniques listed above and to attempt to define present indications and contraindications for closure are the purposes of this communication.

Methods and Material

The literature for the years 1954 through 1956 inclusive was reviewed. Each series of cases of atrial septal defect submitted to surgery and reported in the literature was tabulated. Criteria for appraising results of surgery were established prior to undertaking the study, and the outcome of every case tabulated from the literature was critically evaluated according to these standards, which included:

Good — Complete closure of defect proved by post-operative cardiac catheterization, and/or uncomplicated clinical post-operative course with regression or complete loss of symptoms. General clinical impression that defect was completely closed.

Fair — Some residual interatrial shunting of blood proved by post-operative cardiac catheterization, and/or clinical impression that a small residual shunt existed following surgery although there was

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definite clinical evidence of benefit from operation.

Poor — Large residual interatrial shunt proved by post-operative cardiac catheterization, and/or lack of significant improvement on postoperative clinical evaluation.

On the basis of embryological and post-mortem findings, atrial septal defects historically have been separated into two groups, the ostium primum defects and the ostium secundum defects. This division has been made purely on location, the primum type being lower in the septum and adjacent to the atrioventricular valves and ventricular septum, while the secundum defect is commonly higher in the atrial septum in the region of the foramen ovale or posterior to this landmark.

Recent surgical and pathological investigations[13, 14] have brought to light the fact that the ostium primum defect is nearly always associated with a cleft mitral valve. As Figure 1 demonstrates, this lesion differs only slightly from the complete persistent atrio-ventricularis communis, in which the low atrial septal defect is associated with a high ventricular septal defect and a five-cusped common atrio-ventricular valve.

Brandenburg and DuShane[15] estimate that 10 to 15 per cent of all cases of atrial septal defect are of the atrio-ventricularis communis variety. While the mean age at death in the complete form is only 10 months, patients with partial type commonly reach adult life, many with only the mildest of symptoms. Though the mitral valve is incompetent anatomically, a significant proportion of patients give no hemodynamic evidence of mitral regurgitation.

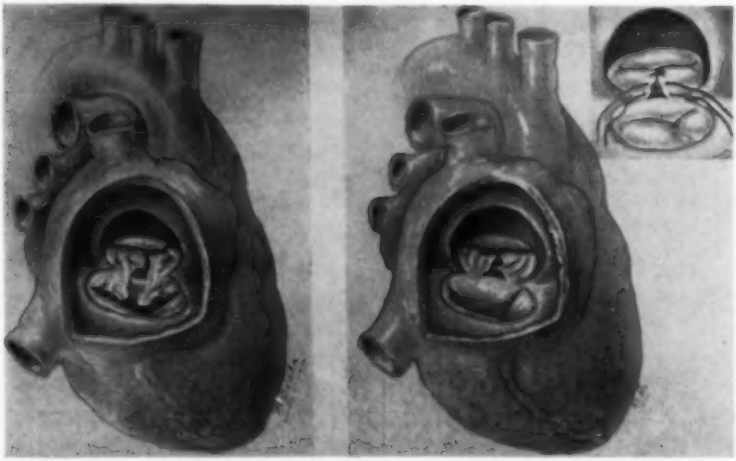


FIGURE 1: Persistent atrio-ventricularis communis. A. Complete form: The defect in the atrial and ventricular septa is visualized. Both atrio-ventricular valves are cleft, the leaflets in reality forming a five-cusped common atrio-ventricular valve. A bare area of muscular ventricular septum is seen forming the inferior margin of the defect. B. Partial form: Only the mitral valve is cleft. The insert demonstrates the technique for repair of the valvular deformity. (From Cooley, J. C., Kirklin, J. W. and Harshberger, H. C.: "The Surgical Treatment of Persistent Common Atrioventricular Canal," *Surgery*, 41:147, 1957.)

TABLE I

SURGICAL CLOSURE OF ATRIAL SEPTAL DEFECT BY ATRIO-SEPTO-PEXY

	Persistent Atrio-Ventricularis Communis						Ostium Secundum Defect						Defect Undifferentiated as to Type					
			Post-Operative Evaluation						Post-Operative Evaluation						Post-Operative Evaluation			
Group	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Evaluation	Cases	Deaths	Good	Fair	Poor	Unevaluated
1. Longmire et al[20]							15	0	11	0	2	2						
2. Husfeldt[22]	2	0	0	1	1	0	4	0	1	0	0	3	6	0	2	0	1	3
3. Kay et al[23]													15	1	0	0	0	14
4. Dahlback et al[27]	2	1	0	0	1	0	7	0	4	2	1	0						
5. Moeys[28]	2	1	0	1	0	0												
6. Bailey et al[1, 26]	16	11	4	1	0	0	57	5	27	2	0	23						
7. Schumacker[29]							1	0	1	0	0	0						
8. Brando et al[17]													2	1	1	0	0	0
TOTAL	21	12 (57.1 %)	4	3	2	0	84	5 (6.0 %)	44	4	3	28	23	2 (8.7 %)	3	0	1	17

The ostium secundum defect arises from abnormal resorption of the septum primum. There results an incompetent valve of the foramen ovale, or, if resorption is too great and growth of the septum secundum is defective, a large defect is produced.[16] This type of communication usually is located centrally or posteriorly in the atrial septum and is separated from the atrio-ventricular ridge by a rim of septal tissue.[17] It is compatible with a longer life span than either form of persistent atrio-ventricularis communis. Roesler[18] reported a mean age at death in 62 cases of 34 years, while Abbott's[19] mean for 55 cases was 31 years.

Present diagnostic techniques cannot distinguish these two lesions before surgery,[14] and results of both forms of persistent atrio-ventricularis communis have therefore been included in this study.

Wherever the literature indicated the type of defect being corrected, this was noted. Often, however, these reports did not give this information, thus requiring three categories for tabulating results of surgical therapy: persistent atrio-ventricularis communis (partial and complete forms), ostium secundum defect, and undifferentiated atrial septal defect.

With slight exception, this survey has been limited to cases of atrial septal defect and persistent atrio-ventricularis communis uncomplicated by further cardiac pathology. The only companion anomaly reported with a significant degree of frequency in the literature was a partial anomalous pulmonary venous return, which was noted in 28 of 281 cases of ostium secundum defect submitted to surgery. Cases with such infrequent companion lesions as pulmonary stenosis, ventricular septal defect, or total anomalous pulmonary venous return were not included in this surgery.

Techniques and Results of Surgical Closure

The four techniques described in the introduction are the methods of closure which have been widely adopted and reported in the literature. Atrio-septo-pexy, circumclusion, and the atrial well technique are all considered "closed" methods of repair in contrast to "open" methods where the operator is allowed to visualize the defect. Each technique will be discussed under individual heading.

Atrio-septo-pexy

This earliest successful technique of repair was not devised with the primary surgical objective of direct anatomic closure of the defect. Rather, Bailey[1] states, the goal was to separate "the two venous systems to the respective atrio-ventricular valves." The redundant anterolateral wall of the dilated right atrium is approximated to the posterior remnant of the septum or to the posterior atrial wall, thus creating a new intracardiac passageway for the flow of vena caval blood. Then, the lateral atrial wall is invaginated against the septum and sutures are placed in the margin of the defect as demonstrated in Figure 2. Accuracy in this procedure is aided by the insertion of the ungloved index finger into the right atrium through an incision in the auricular appendage, the finger then guiding placement of sutures in the septal rim. Schumacker[20] modi-

fied this technique by invaginating a woven nylon pocket sutured to the lateral atrial walls instead of using actual atrial tissue.

Results of atrio-septo-pexy are tabulated and evaluated in Table I. Eight medical centers have reported experience with this method. Bailey feels it is particularly well adapted to treatment of associated mitral stenosis or partial anomalous pulmonary venous return. The presence of the index finger within the heart enables the surgeon to perform a digital commissurotomy of the stenosed mitral valve through the septal defect prior to closure. By approximating the lateral wall only to the anterior margin of the defect, a third chamber is created, and the anomalous right pulmonary veins drain directly into the left atrium through the unclosed defect.

Even a cursory glance at Table I will make the reader aware of the wide gap between the results of surgery in persistent atrio-ventricularis communis and ostium secundum atrial septal defect. The lack of an inferior remnant of atrial septum in the former lesion necessitates placing

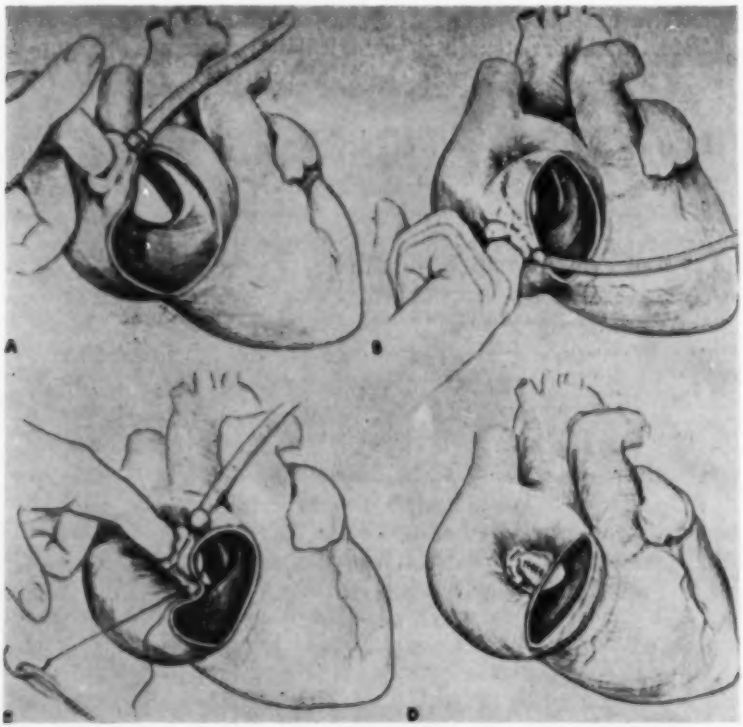


FIGURE 2: Closure of ostium secundum defect by atrio-septo-pexy. A. Digital exploration via right auricular appendage. B. Placement of first suture. C. Approximation of invaginated right atrial wall to periphery of septal defect. D. Completion of atrio-septo-pexy. (From Bailey, C. P., in "Henry Ford Hospital International Symposium on Cardiovascular Surgery," Philadelphia, W. B. Saunders Company, 1955, p. 350.)

sutures in the upper margin of the ventricular septum. This has frequently caused interruption of the common conduction bundle of His and consequent atrio-ventricular dissociation. Bailey attempted to avoid the atrio-ventricular node and bundle by omitting placement of sutures in the ventral portion of the membranous septum. This measure was not successful, however, and this group has abandoned the use of atrio-septo-pexy for closure of atrio-ventricularis communis defects.[28] Others have met with similar results.

Of 84 ostium secundum cases reported, only five succumbed, a mortality of 6.0 per cent. Forty-four of 51 survivors evaluated post-operatively give a clinical impression of complete closure of the defect and consequent regression and loss of symptoms. Bailey repotrs complete closure in 14 of 16 cases catheterized post-operatively with the remaining two persons demonstrating small residual defects which have not prevented marked improvement and benefit from operation. Longmire[21] has recently reported surgical closure by atrio-septo-pexy on 15 cases of ostium secundum defect without mortality. Employing three of the accepted techniques for closure, this group has operated on 34 patients. They state a preference for atrio-septo-pexy over other "closed" methods or repair, terming this the easiest and least hazardous of "closed" techniques.

The 23 cases listed as undifferentiated as to type of defect in Table I included only two deaths, inferring that nearly all were of the ostium secundum variety.

Circumclusion

Eleven medical centers, five of them in Europe, have employed circumclusion or a modification of this technique to close atrial septal defects.

It was Sondergaard[5] who originally conceived the procedure of dissecting a plane of cleavage between the two atria on their posterior aspect. His original work on dogs had demonstrated the presence of a fatty layer separating the atria posteriorly and continuous with the muscular interatrial septum, and he was able to dissect a considerable distance into this fatty septum between the venae cavae and the right pulmonary veins. Bjork and Crafoord[6] introduced the use of the intracardiac finger inserted through the right auricular appendage to aid in passing the circumcluding needle with suture from the upper limit of the cleavage near the base of the aorta through the anterior and inferior margins of the septal remnant and out posteriorly behind the vena cavae. This group first utilized circumclusion on a human patient. Sondergaard[29] later replaced the needle with a blunt flexible probe which is passed around the margin of the defect in the same path, as Figure 3 demonstrates. A suture is tied to the tip of the probe, drawn back through the intraseptal tunnel created by the probe, and then pulled tight thus circumcluding the defect. The suture is tied in the interatrial cleavage plane over a section of plastic, fascia, or muscle. Not only does dissection of this plane aid in accurate placement of the circumcluding suture, but also it prevents obstruction of the superior vena cava or the pulmonary veins when the suture is tied down.

TABLE II
SURGICAL CLOSURE OF ATRIAL SEPTAL DEFECT BY CIRCUMCLUSION
(And Modifications of This Technique)

	Persistent Atrio-Ventricularis Communis						Ostium Secundum Defect						Defect Undifferentiated as to Type					
			Post-Operative Evaluation						Post-Operative Evaluation						Post-Operative Evaluation			
Group	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Unevaluated
1. Bosher[20]							12	0	7	0	0	5						
2. McNamara-Cooley[21]	3	0	3	0	0	0	1	0	1	0	0	0						
3. Edwards et al[22]	4	0	0	4	0	0	7	2	3	2	0	0						
4. Gerbode[23]	1	0	0	1	0	0	4	2	2	0	0	0						
5. Senning[24]							3	0	0	0	0	3						
6. Sondergaard[25]	2	0	0	0	2	0	8	0	8	0	0	0						
7. Husfeldt[26]													21	5	0	0	9	7
8. Walker et al[27]							2	0	1	1	0	0						
9. Southworth-Dabbs[27]	1	0	0	1	0	0												
10. Bjork-Crafoord[28]													12	2	1	0	0	9
11. Lam[29]	4	2	0	0	2	0	12	0	0	0	0	12						
TOTAL	15	2 (13.3 %)	3	6	4	0	49	4 (8.2 %)	22	3	0	20	33	7 (21.2 %)	1	0	9	16

The techniques of Sondergaard and Bjork and Crafoord have been modified to a considerable extent by other workers, but all save one retain the dissection of an interatrial cleavage plane as essential to their methods. Only Edwards[32] does not dissect out this groove. He passes the circumcluding suture directly through the fatty septum. McNamara and Cooley[31] and Bosher[30] reinforce the circumcluding suture by passing interrupted sutures around it in the anterior and inferior rim of the defect, then drawing those sutures back through the cleavage plane and tying them over polyvinyl sponge. Lam,[39] Gerbode,[33] and Senning[34] do not utilize the circumcluding suture, but rather employ various methods of approximating the anterior rim of the defect to the posterior atrial wall in the plane of the cleavage.

Among the advantages of circumclusion, Sondergaard[40] includes the unaltered shape and function of the atria and the lack of exposed sutures or other foreign bodies within the heart. In atrio-ventricularis communis lesions, where the lack of an inferior atrial septal margin requires that the probe or needle be passed through the upper ventricular septum, the fact that it slides parallel to the course of the bundle of His reduces atrio-ventricular conduction difficulties due to method of surgery.

The results of surgical closure of atrial septal defects by circumclusion and related techniques are tabulated in Table II. Despite the lack

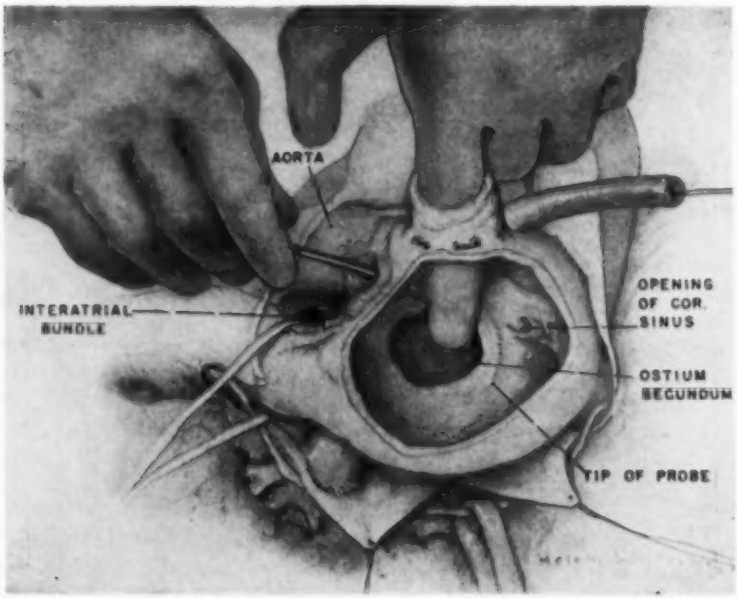


FIGURE 3: Closure of ostium secundum defect by circumclusion. The probe is inserted into the atrial septum at the root of the aorta and guided around the septal margin emerging behind the inferior vena cava. It is then drawn back, carrying with it the circumcluding suture. (From Bosher, L. H., Jr.: "Repair of Interatrial Septal Defects by a Modified Sondergaard Technique (Circumclusion)," *Surgery*, 41:129, 1957.)

TABLE III

SURGICAL CLOSURE OF ATRIAL SEPTAL DEFECT EMPLOYING AN ATRIAL WELL

	Persistent Atrio-Ventricularis Communis						Ostium Secundum Defect						Defect Undifferentiated as to Type					
			Post-Operative Evaluation						Post-Operative Evaluation						Post-Operative Evaluation			
Group	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Unevaluated
1. Bernatz-[46] Kirklin et al[47]	2	0	1	1	0	0	31	1	26	3	1	0	27	2	9	0	0	25
2. Longmire et al[22]							15	2	9	0	2	2						
3. Walker[23]							3	0	2	0	1	0						
4. Muller et al[48]	1	0	0	0	0	0												
TOTAL	3	0 (0.0 %)	1	1	1	0	49	3 (6.1 %)	37	3	4	2	27	2 (7.4 %)	0	0	0	25

of conduction difficulties, only three of 13 survivors with persistent atrioventricularis communis were considered to have complete repair of the deformity on post-operative clinical evaluation. The remaining 10 persons derived little or no benefit from operation.

Mortality in the ostium secundum group was only 8.2 per cent with 22 of 25 survivors demonstrating complete closure on post-operative clinical evaluation.

In 1954, Husfeldt,[41] employing the technique of Sondergaard, reported complete closures of the defect in all survivors in a group of both atrioventricularis communis and ostium secundum cases. In a communication one year later,[22] however, he reported the shunt reestablished in every case on clinical evaluation eight to 21 months after operation. One of these patients was again submitted to surgery; the circumcluding suture was found to have transected the septal tissue, allowing the defect to reopen. No other group has reported this complication.

Atrial Well Technique

The atrial well technique may be regarded as a semi-open method of closure of atrial septal defects. While atrio-septo-pexy and circumclusion allow only one digit to be inserted into the right atrium, this procedure permits the passage of several fingers into the atrial chamber.[42] It has been employed at five medical centers in the United States. Results are tabulated and evaluated in Table III.

The technique as introduced by Gross involves a wide right-sided thoracotomy with the patient in the left lateral position. A clamp is placed on a portion of the lateral wall of the right atrium and a single long incision is made through this pocket of tissue. After a rubber or nylon "well" is sutured to the margins of the incision, the clamp is released and the blood rises slowly into the well (Figure 4). The fingers are passed into the atrial chamber through this pool of blood, allowing, through tactile direction, closure of the septal defect by direct suture or by the onlay of polyethylene sheet shaped to cover the defect. Kirkland,[43, 44] who has operated on the largest series of cases with this method, has modified Gross's technique by administering 300 to 500 cc. of blood to the patient before entering the heart to prevent any effects of sudden blood loss. This group systematically inserts a section of polyvinyl sponge through the well and anchors this to the left side of the septal remnant. The tendency of the blood to flow from left to right across the septum further abuts the sponge against the remnant, aiding in complete closure. With time the sponge is first covered by a layer of fibrin and later converted to a smooth glistening membrane through endotheliazation.[45] Heparin is dripped slowly into the well to prevent clotting of the blood, an injection of protamine after the atrial incision is closed neutralizing the anticoagulant.

In 1955, Watkins and Gross[48] reported the results of surgical repair in 43 cases of atrial septal defect and noted that external suture methods of closure and not the atrial well technique had been employed in the last 30 cases. Kirklin,[46, 47] however, continued to use this method through

early 1956, attaining a total of 60 cases. In 49 cases of ostium secundum defect reported by three groups, there were only three deaths, a mortality of 6.1 per cent. Seven of the 46 survivors have residual shunts of significant degree on post-operative clinical evaluation. Only three persons with persistent atrio-ventricularis communis lesions have been submitted to this technique of repair. While there was no mortality, two of the three received little or no benefit from surgery.

FIGURE 4: The atrial well technique. A. Position of chest wound. B. Attaching a rubber "well" to the wall of the right atrium. C. With the well in place, the atrial wall opened widely at its base, the fingers are inserted through the pool of blood into the atrial chamber, and the septal defect may be closed. (From Gross, R. E. and Watkins, E., Jr.: "Surgical Closure of Atrial Septal Defects," *A.M.A. Arch. Surg.*, 67:670, 1953.)

Direct Vision Techniques

Within a year of the introduction of atrio septo-pexy, Lewis[8] had achieved successful closure of an atrial septal defect in an open heart under hypothermia. Experimental research with temporary occlusion of the flow into the heart in order to obtain an open dry field had been conducted as long ago as 1907 by Haeker.[50] Application of this procedure to surgery on the human heart had been limited by the rapid ischemic effects on the tissues, especially the brain and central nervous system. By reducing tissue oxygen consumption, however, low body temperature has permitted occlusion of the venae cavae for short periods of time and opened the way for direct vision intracardiac surgery.

Several techniques for cooling the body have been utilized in closure of atrial septal defects. Kimoto[51] cannulates the common carotid artery, drawing the blood through a heat exchange coil submerged in a refrigerant and thus cooling the brain. Nine cases of atrial septal defect, three described specifically as ostium secundum and six undifferentiated as to type, have been submitted to surgery. There has been no operative mortality, and all nine patients demonstrate complete closure on clinical post-operative evaluation.

Lewis,[52] Swan,[53] Salyer,[55] and Longmire[21] have employed surface cooling techniques to induce hypothermia. The anesthetized patient is immersed in ice water until his body temperature falls to the desired level for surgery. Lewis has worked within a range of 24.5 to 29.5 degrees Centigrade, while Swan and Longmire and Salyer prefer somewhat higher temperatures. Even at 31 degrees Centigrade, tissue oxygen consumption is only 55 per cent of normal.[54] All direct vision methods require a bilateral thoracotomy, transecting the sternum. Occlusion of the venae cavae is limited to a period of less than eight minutes. The right atrium is incised widely and the defect is repaired, employing continuous suture approximation of the margins of small defects and polyethylene or polyvinyl sections to close larger openings. The limited period of inflow occlusion prevents suture approximation of the two leaflets of the cleft mitral valve in persistent atrio-ventricularis communis. After closure of thoracotomy incision, the patient is rapidly rewarmed to near normal body temperature.

These five groups have used hypothermia for direct-vision closure of 93 cases of ostium secundum atrial septal defect (Table IV). Although there have been 11 deaths due to operation, 50 of 53 patients evaluated post-operatively have demonstrated complete abolition of the shunt, and there have been no poor results in this group. The outcome in 10 cases of persistent atrio-ventricularis communis has not been nearly as encouraging; there have been only four survivors and only one of these appears to have had complete repair of his deformity. Both Lewis and Swan report a tendency for patients in the hypothermic state to go into ventricular fibrillation, and this is cited as the cause for several of the operative deaths. Induction of respiratory alkalosis by administration of carbon dioxide or injection of prostigmine into the sino-atrial node

TABLE IV
SURGICAL CLOSURE OF ATRIAL SEPTAL DEFECT BY DIRECT VISION TECHNIQUES

Group	Persistent Atrio-Ventricularis Communis						Ostium Secundum Defect						Defect Undifferentiated as to Type					
			Post-Operative Evaluation						Post-Operative Evaluation						Post-Operative Evaluation			
	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Unevaluated	Cases	Deaths	Good	Fair	Poor	Unevaluated
Hypothermia:																		
1. Swan-Blount[37]	4	2	1	0	1	0	45	7	26	1	0	11						
2. Salyer et al[35]							12	1	10	1	9	0						
3. Longmire et al[33]							4	0	0	0	0	4	6	0	6	0	0	0
4. Kimoto et al[31]							3	0	3	0	0	0						
5. Lewis et al[32]	6	4	0	2	0	0	29	3	11	1	0	14	6	0 (0.0 %)	6	0	0	0
Subtotal	10	6 (60.0 %)	1	2	1	0	93	11 (11.8 %)	50	3	0	29						
6. Lillehei et al[19]	4	3 (75.0 %)	1	0	0	0												
Pump-Oxygenator:																		
7. Dennis[36]													1	0	1	0	0	0
8. Cooley-Kirklin[39]	9	2	7	0	0	0												
9. Lillehei[37]	11	7	4	0	0	0	6	0	6	0	0	0						
Subtotal	20	9 (45.0 %)	11	0	0	0	6	0 (0.0 %)	6	0	0	0	1	0 (0.0 %)	1	0	0	0
TOTAL	34	18 (52.9 %)	13	2	1	0	99	11	56	3	0	29	7	0 (0.0 %)	7	0	0	0

are proposed as means of preventing this complication, but neither procedure has yet been clearly substantiated by clinical trial. Swan[58] also reports transient peripheral neuropathies in twelve patients following

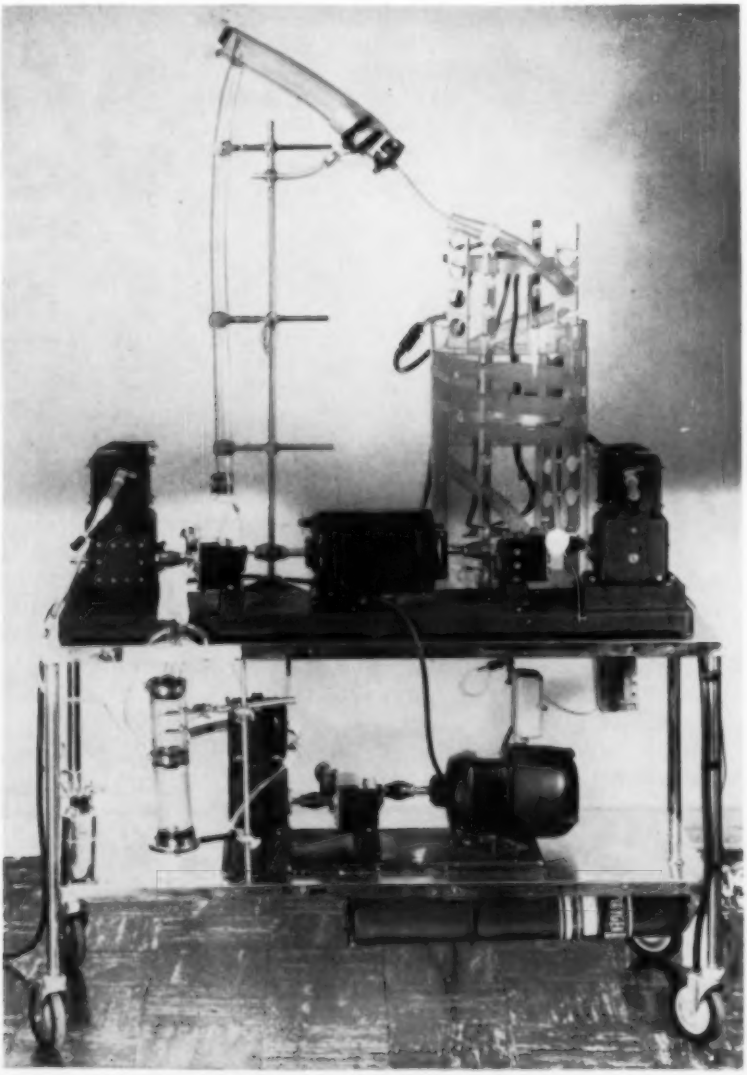


FIGURE 5: The DeWall pump-oxygenator. Essential parts as shown include an explosion-proof motor, arterial and venous pump heads, a vertical mixing tube, and inclined debubbling chamber, and the helix reservoir immersed in a constant temperature water bath. The oxygen gas enters the venous blood directly through a nylon diffusion plate at the base of the mixing tube. Venous carbon dioxide escapes with excess oxygen during oxygenation.

intracardiac surgery under hypothermia and warns of blood coagulation abnormalities below 28.5 degrees Centigrade.

Various experimental attempts have been made to substitute an extracorporeal circulation for the patient's heart and lungs, relieving these organs of the obligation to oxygenate the blood and circulate it to the tissues and allowing the surgeon to work in a bloodless heart for longer periods than hypothermia permits. One of the most interesting of these methods to be given clinical trial was controlled cross circulation. Lillehei and Varco,[59] utilizing a human donor to oxygenate the patient's blood, closed the septal defects and repaired the valvular deformity in three cases of persistent atrioventricularis communis. Unoxygenated blood from the patient's venae cavae was drawn by catheters into the donor's great saphenous vein, and oxygenated blood was returned from the donor's superficial femoral artery to the patient's subclavian artery. Auxiliary pumps and an arterial blood reservoir were interposed between the two circulations. The one survivor of this procedure demonstrated complete closure of the defect and abolition of valvular regurgitation on post-operative cardiac catheterization.[10]

At present, the most advanced refinement of the extracorporeal circulation is the mechanical pump-oxygenator as originally proposed by Gibbon in the mid-thirties.[60] The venae cavae and the aorta are cannulated and occluded and the catheters are connected to the pump-oxygenator. During the past two years, three different pump-oxygenators have been employed in the closure of atrial septal defects. Dennis[56] and Kirklin[61] use apparatus in which a film of blood less than a millimeter in thickness flows over fine mesh screen within an oxygenating chamber. Kirklin employs parallel rectangular vertical screens according to the scheme of Gibbon, while Dennis uses four rotating screen discs. Lillehei[11] utilizes a vertical plastic oxygenator (Figure 5), the blood mixing with large bubbles of pure oxygen. This group has shown that the patient can and does survive surgery without ill effect while the pump-oxygenator circulates less than one half the usual cardiac output of a normal human of similar size.

With the pump-oxygenator there is no limit to the period of occlusion of the vessels leading to and from the heart.[56] This allows location and repair of valvular deformities in cases of persistent atrio-ventricularis communis. By avoiding placement of stitches in the posterior half of the ventricular septum and at the posterior junction of the atrial septum and the atrio-ventricular valves, interference with the common conduction bundle may be averted,[12] and the septal defects may be closed with fewer complications. The valvular deformity is repaired (Figure 1*b*) and the defect is closed by continuous suture approximation of its margins or by anchoring a polyvinyl section to the septum with interrupted sutures. Results have been equivocal in the first 20 cases. While mortality has exceeded 40 per cent, the eleven survivors all demonstrate complete repair of this complex anomaly on post-operative clinical evaluation.

There has been no mortality in six cases of ostium secundum atrial

septal defect closure with the pump-oxygenator; all six patients demonstrate complete closure post-operatively.[37]

Ostium Secundum Atrial Septal Defect

All of the techniques described above for repair of ostium secundum atrial septal defects have been employed with success (Table V). Only five years after the first successful closure, the operative mortality in any of the accepted procedures approximates one case in 10 or better.

To give the seal of approval to one of these techniques to the exclusion of the other three would be a mistake. Each has its own advantages and disadvantages as enumerated above. Theoretically, it would appear that direct vision techniques which allow the operator to visualize his field would be preferable to the "closed" methods. To a certain degree, this is true; among survivors, "open heart" procedures have yielded only one-half as many fair and poor results as the "closed" techniques. However, the mortality in atrio-septo-pexy and atrial well closures is only slightly more than one-half that of the direct vision procedures.

Only Husfeldt[22] has reported serious post-operative complications. All of his cases demonstrated reestablishment of the interatrial shunt on post-operative clinical evaluation. It is believed that the circumcluding suture pulled through the septal tissue in these cases. In view of this, and despite the successful results reported by Bjork and Crafoord,[38] Sondergaard,[35] and others in 1954 and 1955, the technique of circumclusion must be regarded with some degree of suspicion until more cases are available for later post-operative evaluation. Perhaps, the reinforcing suture as utilized by McNamara and Cooley[31] and Bosher[30] will prevent transection of the septal tissue by the circumcluding suture and insure complete permanent closure of the defect.

It is self-evident that the methods of closure employing circumclusion and the atrial well require highly skilled operators, practiced in the most minute of digital movements. Atrio-septo-pexy is perhaps the "closed" method most adaptable to widespread use involving the least special equip-

TABLE V

RESULTS OF SURGICAL CLOSURE OF OSTIUM SECUNDUM ATRIAL SEPTAL DEFECT

Method	Cases	Deaths	Per Cent Mortality	"Good" Results / Total Cases Evaluated
Atrio-septo-pexy	84	5	6.0	44/51
Circumclusion	49	4	8.2	22/25
Atrial Well	49	3	6.1	37/44
Direct Vision	99	11	11.1	56/59
TOTAL	281	23	8.2	159/179

ment and training. Direct vision techniques relieve the surgeon of dependence on tactile sensation, but require highly skilled operating room teams.

At present, the use of hypothermia introduces the possibility of severe cardiac arrhythmias and transient post-operative neuropathies. It is not beyond the realm of probability to assume that vigorous pharmacological and physiological research will soon overcome these complications, but they must be considered in evaluating and comparing present operative techniques.

Utilization of the pump-oxygenator provides the most promise for the future. Here the surgeon can work in an "open heart" for long periods of time. There have been a minimum of post-operative complications in Lillehei's six patients,[57] but a much larger group of cases is needed before this method can be properly evaluated.

Persistent Atrio-Ventricularis Communis

There is still small cause for optimism in the surgical picture of persistent atrio-ventricularis communis. Because of the valvular deformities involved in both the partial and complete forms of this anomaly, it is difficult to understand how "closed" methods of repair, which do not permit suturing of the cleft valve or valves, can lead to "good" results on post-operative evaluation. It must be assumed that the eight cases demonstrating complete abolition of the shunt and regression or loss of symptoms post-operatively as reported in the literature[31,37] were instances of the rare ostium primum defect without involvement of the atrio-ventricular valves or were examples of the situation reported by Cooley and Kirklin where the cleft mitral valve was physiologically competent.

Critical appraisal of the statistics in Table VI verifies the statement that direct vision methods of repair of persistent atrio-ventricularis communis are the only procedures which will benefit the majority of survivors. The lesion is complex and the partial form cannot yet be distinguished from the complete form pre-operatively. Thus, the limited period of

TABLE VI

RESULTS OF SURGICAL CLOSURE OF PERSISTENT ATRIO-VENTRICULARIS COMMUNIS

Method	Cases	Deaths	Per Cent Mortality	"Good" Results / Total Cases Evaluated
Atrio-septo-pexy	21	12	57.1	4/9
Circumclusion	15	2	13.3	3/13
Atrial Well	3	0	0.0	1/3
Direct Vision	34	18	52.9	13/16
TOTAL	73	32	43.8	21/41

inflow and outflow stasis in open cardiotomy under hypothermia is inadequate for identification of the nature of the deformity and its appropriate repair (see Table IV). Cross circulation was abandoned in favor of the pump-oxygenator as a method of cardiopulmonary bypass because of the risk to two patients instead of one. The latter instrument has met with high mortality in the first 20 cases. It is significant, though, that all 11 survivors demonstrate complete correction of the deformity on post-operative clinical evaluation. It seems fair to assume that mortality will decline as the number of cases submitted to surgery increases. At this time, however, either form of persistent atrio-ventricularis communis carries only a "50-50" prognosis for recovery from surgery in contrast to a "90-10" prognosis in cases of ostium secundum atrial septal defect.

SUMMARY AND CONCLUSIONS

Within the past five years, four techniques of successful surgical correction of defects in the atrial septum have been introduced and employed in significant numbers of cases. These include atrio-septo-pexy, circumclusion, closure through an atrial well, and direct vision correction in the "open" heart.

A survey of the literature for the three year period 1954 through 1956 disclosed 444 cases of atrial septal defect submitted to surgery and evaluated on a clinical or physiologic basis post-operatively; 281 cases were of the ostium secundum type, 73 cases were of the persistent atrio-ventricularis communis variety (partial or complete forms), and 90 cases were undifferentiated as to type of defect in the published reports.

Techniques for surgical closure are described and results as reported in the literature are evaluated. All methods of closure of the ostium secundum defects have met with success; the overall mortality in the 281 cases evaluated was 8.2 per cent. Direct vision procedures employing hypothermia or a pump-oxygenator to permit stasis of the circulation to and from the heart and thus allow visualization of the defect have yielded the highest percentage of complete closures but are presently associated with the highest mortality rate among the four evaluated techniques. The complex nature of persistent atrio-ventricularis communis deformities requires long periods of work in the "open" heart, necessitating use of a pump-oxygenator for cardiopulmonary bypass. Results in the first 20 cases are equivocal; there were nine deaths, but the remaining 11 patients all demonstrate complete correction of the deformity.

Acknowledgment: The author wishes to express his sincere appreciation for the invaluable criticism and guidance of Dr. Paul Adams, Jr., Assistant Professor of Pediatrics, University of Minnesota Medical School, without whose encouragement this paper would likely not have been completed.

RESUME

Pendant les cinq dernières années, quatre techniques de correction chirurgicale satisfaisante des défauts de la paroi de l'oreillette ont été introduites et utilisées dans un grand nombre de cas. Elles comprennent l'atrio-septo-pexie, la compression artérielle, la fermeture à travers la

paroi de l'oreillette et la correction par vision directe dans l'opération à "coeur ouvert".

Une revue de la littérature pendant une période de trois ans, de 1954 à 1956, met en lumière 444 cas de malformations de la paroi de l'oreillette soumises à la chirurgie, et recensées après l'opération sur une base clinique et physiologique. 281 cas étaient du groupe de la communication interauriculaire, 73 cas étaient de la variété commune de la persistance du trou de Botal (formes complètes ou partielles) et 90 cas étaient indifférenciés, quant au type de malformation publiée.

L'auteur décrit les techniques de fermeture chirurgicale et discute les résultats tels qu'ils sont rapportés dans la littérature. Toutes les méthodes de fermeture des communications interauriculaires ont été accomplies avec succès. La mortalité moyenne dans les 281 cas fut de 8,2%. Les procédés de vision directe utilisant l'hyopthermie ou une pompe oxygénatrice pour permettre le maintien de la circulation à l'arrivée et au départ du coeur et la constatation de la malformation ont comporté le pourcentage le plus élevé de fermetures complètes, mais ils sont actuellement redevables du taux de mortalité le plus élevé sur les quatre techniques estimées. La nature complexe des malformations lors de la persistance du trou de Botal exige un travail longtemps prolongé à "coeur ouvert" nécessitant l'emploi d'un oxygénateur à pompe pour assurer le transit cardio-pulmonaire. Les résultats des premiers vingt cas sont à demi satisfaisants; il y eu neuf décès, mais les onze malades restants ont tous donné la preuve d'une correction complète de leurs malformations.

RESUMEN Y CONCLUSIONES

En los pasados cinco años se han introducido y empleado en un número significativo de casos, cuatro técnicas de corrección satisfactoria de los defectos del septum atrial. Ellos incluyen la atrio-septo-pexia, la cirnun-inclusión, las clausuras a través de un poso atrial y la corrección bajo visión directa en corazón abierto.

Una revisión de la literatura para los tres años de 1954 hasta 1956 permitió encontrar 444 casos de defecto atrial septal operados y estimados sobre bases clínicas, y fisiológicas postoperatoriamente; 281 casos fueron del tipo ostium secundum; 73 de la variedad atriventricular común (formas parciales o completas) y 90 fueron indiferenciados respecto del tipo en las publicaciones.

Se describen las técnicas de clausura quirúrgica y los resultados según la literatura se valúan.

Todos los métodos para cierre del tipo ostium secundum fueron de buenos resultados; la mortalidad global en 281 casos fué de 8.2 por ciento.

Los procedimientos de visión directa usando hipotermia o una bomba con oxigenador para permitir detención de la circulación de y hacia el corazón y así permitir la vista del defecto, han dado el porcentaje mayor de clausuras completas pero por ahora se asocian a la mortalidad mayor entre las cuatro técnicas consideradas.

La naturaleza compleja del defecto atriventricular persistente común requiere largo tiempo de trabajo en el corazón abierto necesitándose el

oxigenador con bomba para la desviación de la circulación. Los resultados en los primeros 20 casos no son francos porque hubo nueve muertes pero en los 11 restantes, todos obtuvieron completa corrección de la deformidad.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Im Verlauf der letzten 5 Jahre wurden 4 Techniken einer erfolgreichen chirurgischen Behebung von Vorhof-Septumdefekten entwickelt und in einer beträchtlichen Zahl von Fällen zur Anwendung gebracht. Zu diesen Verfahren gehören: Vorhof-Septum-Anheftung, Zirkumklusion, Verschluss durch eine Vorhofswand und Korrektur unter direkter Sicht am "offenen" Herzen.

Eine Literatur-Übersicht der 3-Jahresperiode von 1954 bis Ende 1956 ergab 444 Fälle von Vorhof-Septumdefekt mit chirurgischer Behandlung, die postoperativ auf klinischer oder physiologischer Basis ausgewertet wurden; 281 Fälle gehörten dem Typ des ostium secundum an, 73 Fälle der Varietät des persistierenden gemeinsamen Vorhof-Ventrikels (partielle oder komplette Formen), und 90 Fälle waren in den veröffentlichten Berichten nicht aufgegliedert hinsichtlich der Art des Defektes.

Die Methoden für den chirurgischen Verschluss werden beschrieben und die Ergebnisse and Hand der Literatur-Berichte ausgewertet. Alle Verfahren des Verschlusses der Ostium-secundem-Defekte waren erfolgreich. Die Gesamt-Mortalität der 281 ausgewerteten Fälle betrug 8,2%. Die Methoden unter direkter Sicht, die die Unterkühlung oder die Sauerstoff-Versorgung durch Pump-System anwandten zur Ermöglichung eines Stillstandes der Zirkulation zum und vom Herzen und die auf diese Weise die direkte Darstellung des Defektes gestatteten, ergaben den höchsten Prozentsatz kompletter Verschlüsse, sind aber gegenwärtig verknüpft mit den höchsten Mortalitäts-Ziffern der 4 ausgewerteten Prozeduren. Die komplexe Naturder persistierenden formitäten des atrio-ventricularis communis erfordert langes Arbeiten am "offenen" Herzen und macht so die Benutzung eines Pumpen-Oxygenators für den cardio-pulmonalen Nebenschluss erforderlich. Die Resultate der ersten 20 Fälle sind zweifelhaft mit 9 Todesfällen, während die restlichen 11 Patienten sämtlich eine vollständige Behebung der Missbildung aufwiesen.

References will appear in reprints.

ELECTROCARDIOGRAM OF THE MONTH

Angina Pectoris and Premature Systoles Induced by Exercise

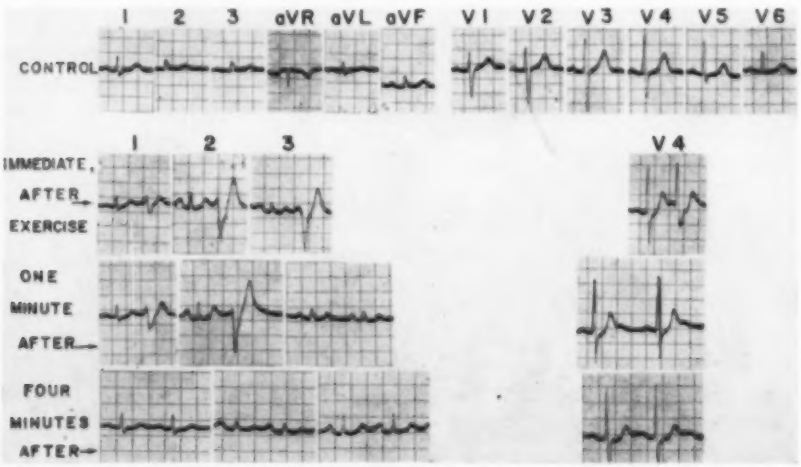
The author would be pleased to receive comment and controversy from readers in relation to explanations offered

A 39 year old railroad brakeman gave a one month history of midsternal "raw feeling" radiating to the lower anterior one-third of the neck. This sensation was never described as a pain or a pressure. It usually occurred after walking a quarter of a mile. Sometimes he could walk three miles without this symptom. It always disappeared after rest. Both parents have heart disease but three brothers do not. Physical examination was entirely negative. The blood pressure was 130/80.

Cardiac fluoroscopy and x-ray showed a normal cardiac silhouette without ventricular enlargement. The serum cholesterol was normal. The clinical impression was angina pectoris because of the site and radiation of the chief complaint.

At this age, collateral evidence is welcome and hence a two step exercise test was performed. Immediately after exercise, the S-T segment in Lead IV (see illustration) was depressed almost 1 mm. This is abnormal according to Master's criterion but not by the standards of other investigators. Hence this finding alone might not be sufficient evidence.

Immediately after exercise there developed coupled premature ventricular systoles from one focus constituting a pulsus bigeminus which disappeared after one minute (see illustration). The literature on premature



ventricular systoles, whether coupled or not, produced by exercise is not extensive but the evidence indicates that they are usually, although not invariably, associated with coronary insufficiency. They were so interpreted in this patient (who had no previous history of premature contractions). Interestingly enough, the patient developed at the end of the exercise test a "raw feeling" in the midsternum suggesting that this complaint is the "equivalent" of pain for this particular patient.

Thus the following data are available: a suspicious history and the occurrence of the main complaint after exercise; S-T segment depression in a precordial lead; coupled premature ventricular systoles precipitated by the two-step exercise test. This evidence was interpreted as corroborating the initial impression of angina pectoris.

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Case Report Section

Paroxysmal Pseudoventricular Fibrillation

(Paroxysmal Atrial Fibrillation with Accelerated Atrioventricular Conduction)

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The present report concerns a patient who was successfully treated for paroxysmal pseudoventricular fibrillation with procaine amide (pronestyl) intravenously. This unusual electrocardiographic pattern occurs in healthy young individuals with no clinical evidence of heart diseases. Recently, Hermann, et al. reported six cases of paroxysmal pseudoventricular fibrillation in young individuals.[10]

The patient was a 34 year old white man, admitted to the hospital on February 13, 1957. He complained of palpitation and heaviness in his chest. He was well until one hour before admission. While talking by telephone, he noted the onset of palpitation. There was no dyspnea, chest pain, weakness or dizziness. System review was entirely negative. His first attack had occurred at the age of 24 while playing basketball. Since then similar spells occurred approximately once or twice a year. Invariably the attacks were associated with physical activity, would last for a few minutes and disappear after he laid down. There was no history of rheumatic fever, chorea, scarlet fever or diphtheria. The family history was not contributory. He drank two cups of coffee and smoked a package of cigarettes daily. Physical examination revealed a well developed young white man in no acute distress. There was no cyanosis or dyspnea. The temperature was 99° F. The radial pulse was 240-260 per minute. The examination of the eyes, ears, nose and throat was normal. The neck veins were not distended and the thyroid was not enlarged. The lungs were normal to auscultation and percussion. The heart was not enlarged. There were no murmurs or thrills. The rhythm was slightly irregular at a rate of 240 per minute. The blood pressure was 115 mm. Hg. systolic and 80 mm. Hg. diastolic. The radial pulse was weak and thready. The remainder of the physical examination was essentially negative.

The urinalysis was normal. The white blood cells numbered 11,600 per cu. mm.; of the leukocytes the lymphocytes were 16 per cent, the monocytes 7 per cent, the neutrophils 69 per cent, stabs 7 per cent, and the eosinophils 15. The sedimentation rate was 26 mm. per hour (Westergren).

On admission, the electrocardiogram (Figure 1A) was interpreted as a paroxysmal ventricular tachycardia. There was an unusually high ventricular rate of 240 per minute with slight irregularity and many bizarre ventricular complexes. Carotid sinus stimulation was ineffective. It was decided to give procaine amide (pronestyl) intravenously. The initial dose of 200 mg. was given slowly with no untoward effects. In about 120 minutes the entire dose of 800 mg. was given at which time the heart action was restored to the sinus rhythm (Figure 1B). The P-R intervals were very short (0.06-0.08 second) and the initial portion of the up stroke of the R wave was slurred producing a delta R type wave such as is seen in accelerated atrioventricular conduction. He had no complaint and it was decided to place him on oral quinidine sulfate 0.2

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Acknowledgment: We are deeply indebted to Charles Kosmann, M.D., New York University, Bellevue Medical Center, for his review of the electrocardiograms.

grams four times daily. Every other day an electrocardiogram was taken without changes and he recovered completely. There was no recurrence of tachycardia during 13 days of hospitalization and he was discharged without any cardiac symptom. The heart was not enlarged and no abnormal sound was heard after the attack was over.

DISCUSSION

This unusual electrocardiographic pattern occurs in healthy young individuals with no clinical evidence of heart disease, whose only complaints are paroxysmal rapid heart action.[7] In spite of these bizarre electrocardiographic findings these patients are comfortable and their blood pressures are well maintained. This syndrome is thought to be benign. The electrocardiogram pattern may be produced by two conditions; paroxysmal tachycardia with atrial fibrillation in a patient with accelerated A-V conduction and tachycardia with false bundle branch block.[10] In 1930 Wolff-Parkinson and White described the syndrome of the short P-R interval with an abnormal QRS complex and paroxysmal tachycardia. It occurred especially in young individuals with normal hearts. The paroxysmal rapid heart action is always of the supraventricular variety. Atrial fibrillation and flutter may also occur.[5] Paroxysmal heart action occurs in at least 70 per cent of all cases of the Wolff-Parkinson and White syndrome.[5] Prinzmetal et al.[5] report experimental and clinical evidence of accelerated conduction through the atrioventricular node. Paroxysmal ventricular

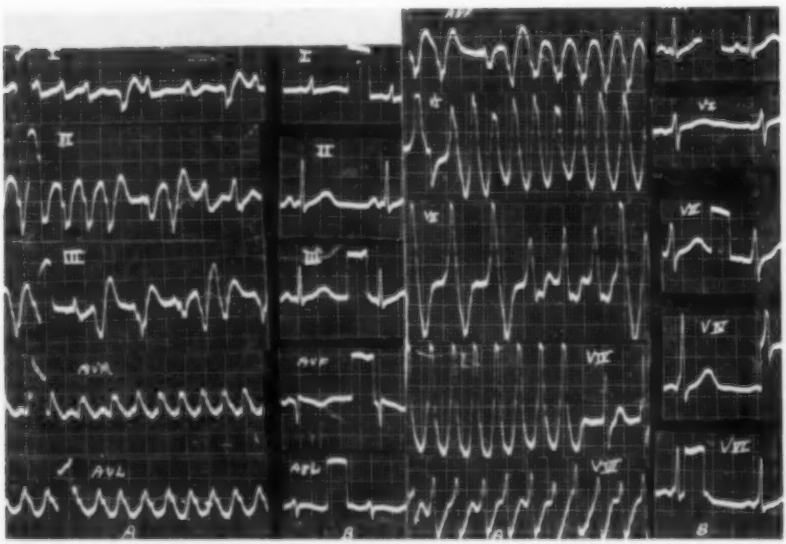

FIGURE 1A FIGURE 1B

Figure 1A: Electrocardiogram taken during the attack, showing pseudoventricular fibrillation at the rate of 240 per minute.—*Figure 1B:* After 800 mgm. Procaine Amide (Pronestyl) given intravenously, shows aberrant QRS complexes, short P-R interval, and slurred uptake R-Delta waves, without P-waves showing the underlying atrial fibrillation.

tachycardia has been described as of rare occurrence in association with the Woff-Parkinson and White syndrome.[3] With ventricular tachycardia the rhythm is practically regular and the P-R interval is constant. Carotid stimulation does not affect the rate in ventricular tachycardia, but it may slow or terminate an attack of supraventricular tachycardia.[8] The tachycardia of regular rhythm with Wolff-Parkinson and White syndrome and regularly placed P-waves on each wide QRS and the presence of a few narrow QRS complexes are the diagnostic criteria of paroxysmal pseudoventricular tachycardia.[10] Absolutely irregular rhythm with no P-waves and occasional short runs of narrow QRS interval with a high ventricular rate of over 200 indicates atrial fibrillation with false bundle branch block or pseudoventricular fibrillation of the Wolff-Parkinson and White syndrome. The prognosis is generally excellent but in rare cases, patients have died in paroxysmal tachycardia with fibrillation. Procain amide (pronestyl) is the drug of choice and it must be given slowly intravenously

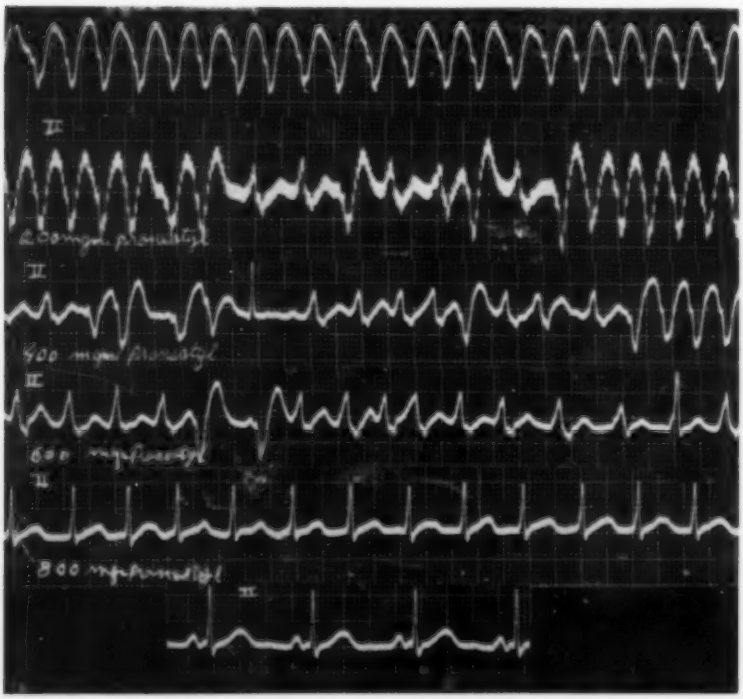

FIGURE 2: Shows Pseudoventricular fibrillation at the rate of 240 per minute. Intermittent portions of continuous strip of standard lead II, during intravenous administration of procain amide (pronestyl). After 800 mgm. of pronestyl was given, the rate slowed to 140 per minute and an irregular rhythm without P-waves (atrial fibrillation) occurred. At the bottom standard lead II shows a normal rhythm with aberrant QRS complexes (slurring of the upstroke of the R-wave) and short P-R intervals (WPW Syndrome).

and with constant electrocardiographic observation and frequent blood pressure determinations. Quinidine sulfate may be used but it is our belief that it is dangerous when given intravenously because it may cause cardiac standstill. Digitalis should not be given as it may be harmful because of a possible increase of ventricular irritability.

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Reversible Angina Pectoris*

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It has been demonstrated repeatedly that not much importance can be attached to the prognostic significance of bundle branch block. Right bundle branch block has been considered to show a more favorable prognosis than left bundle branch block. However, the presence of right bundle branch block, either the typical or atypical form, alerts the physician to the basic cardiac disease, particularly disease of the coronary circulation. Bundle branch block may occur transiently or it may be permanent. Generally, when bundle branch block is associated with coronary atherosclerosis, it is persistent.

The following case is reported because of the association of the presence of bundle branch block with symptoms indicative of coronary artery disease and the subsequent disappearance of symptoms and electrocardiographic abnormalities on a specific dietary regimen. Of interest are the therapeutic implications associated with the disappearance of symptoms and bundle branch block.

The patient was a 46 year old, white pharmacist who presented himself on October 28, 1954 because of an increasingly severe angina pectoris syndrome. He stated that for a period of about one year, he had experienced left anterior chest pain with effort. The pain usually came on while working and was relieved by sublingual nitroglycerin pills. Being a pharmacist, he had tried a number of coronary vasodilator drugs, but none afforded relief. He presented himself with regard to limiting hours of work since his tolerance seemed to be decreasing. The family history was negative for diabetes and cardiac disease.

Examination was not remarkable other than for the presence of xanthoma tuberosum lesions covering the extensor surfaces of both elbows. The ocular fundi showed silvering of the arterioles. He was 67 inches tall and weighed 164 pounds. Blood pressure was 118/68. Heart sounds were normal and no murmur was heard. A2 was greater than P2. Examination of the lungs and abdomen was negative. An electrocardiogram showed the presence of atypical right bundle branch block. Ballistocardiographic study showed an abnormal pattern. Laboratory examinations were not revealing other than the cholesterol value of 345 mgm./100 cc. of blood.

Because of the presence of the xanthoma tuberosum and the elevated blood cholesterol level, he was placed on a low-fat, low-cholesterol diet along with a lipotropic capsule to be taken twice daily. When seen two months later, there was no change in symptoms or electrocardiogram findings (Fig. 1). He was following the low-fat, low-cholesterol diet and continued to follow it, despite severe restrictions upon his eating habits.

On November 7, 1955, the patient reported that he had followed the dietary regimen throughout the year. He was no longer having chest pain with effort. In addition to his usual, full-time job as a pharmacist, he was doing additional work. He now weighed 158 pounds and the physical examination was not remarkable. Blood pressure was 144/82. The blood cholesterol was 206 mgm./100 cc. of blood. Electrocardiographic examination at this time showed a completely normal pattern. The right bundle branch block was no longer present (Fig. 2). Subsequent examinations have confirmed the presence of a normal electrocardiographic pattern and he remains completely well. He has required no nitroglycerin or other medication since following the diet. There has been a moderate decrease in the size of the xanthoma tuberosum lesions of his elbow.

Etiology of Atherosclerosis

While there has not been a change in the high incidence of atherosclerosis in the United States or in the excessively high death rate due to

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atherosclerosis, there has been a marked change in the attitude of physicians towards this disease; physicians and patients alike have assumed a more hopeful outlook. Such change in attitude is due to the realization that the concept of atherosclerosis being a physiological aging process is erroneous. The present concept of the atherosclerosis problem is the appreciation that it is basically a metabolic disease.

There has been a recent realization that atherosclerosis may be preventable or possibly even reversible.[1] To reverse the process would result in a tremendous reduction in morbidity and mortality rates in our country as a result of decreasing the incidence of atherosclerosis, the greatest cause of death in the middle aged and elderly.[2] All investigations seem to point to the fact that atherosclerosis is primarily a metabolic disease, particularly such metabolism as concerns the cholesterol-lipid-lipoprotein relationship in the human body. Although much of the work emphasizes that the typical American diet, which is high in cholesterol, lipids and calories, is an important etiological factor in atherosclerosis, no attempt has been made to incriminate diet as the only operating mechanism. Other contributing factors in the pathogenesis of atherosclerosis are heredity, physical activity, stress, sex and other metabolic diseases such as diabetes, nephrosis and familial hypercholesteremia.

In attempting to study why man is unique among mammals in his predisposition to form atheromatous patches in blood vessels, attention has been focused on the chemical factors. If the abnormalities of lipid composition associated with atherosclerosis are to be altered in the direc-

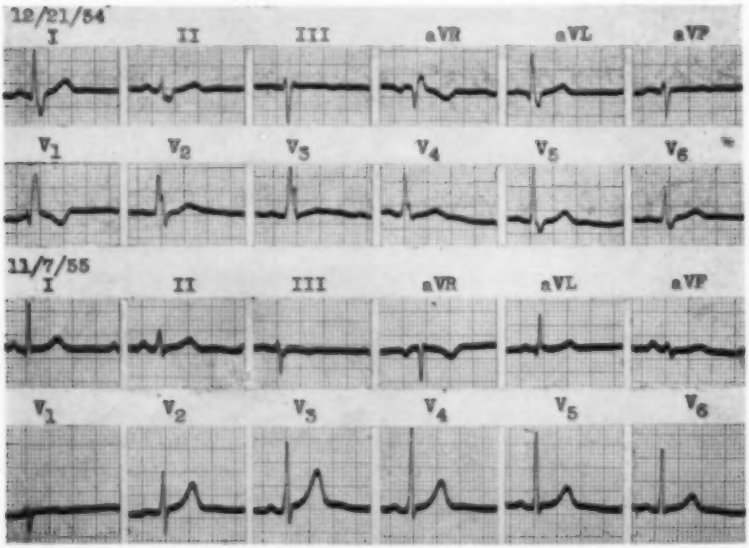

FIG. 1

FIG. 2

Figure 1: Electrocardiogram taken December 21, 1954 showing atypical right bundle branch block—Wilson type.—*Figure 2:* Electrocardiogram taken November 7, 1955 showing a normal pattern. At this time the patient was free of chest pain.

tion of the conditions found in young women and in mammals immune from atherosclerosis, one may use the dietary approach which indicates a low-fat, low-cholesterol diet or follow Barr's approach, which has been the use of female sex hormones.[3] While workers previously had attempted to lower serum cholesterol and to alter lipid metabolism by means of diet, the scientific stimulus in this direction resulted from the studies of Keys,[4] who showed that an outstanding feature of all populations known to have relatively little coronary heart disease is the low consumption of fats. Experiments in man have shown that fat, and not the cholesterol content of the diet, has a strong effect on blood cholesterol. Low-fat diets have also been shown to reduce the incidence of thromboembolic disease. In Norway, during World War II, the decline of incidence in coronary artery disease mortality was paralleled by a sharp decline in thromboembolic complications after surgery. These declines in mortality and morbidity have been held to be due to the low-fat diet prevalent at the time.[4] Another study which indicated a relationship between plasma lipids and coronary atherosclerosis was that of Enos, who reported on American soldiers killed in Korea.[5] Gertler's studies also indicated a causal relationship between atherosclerosis and elevated serum cholesterol.[6] Confirmation of this study is seen in the studies of H. Steiner, who also noted that the high cholesterol level in patients with atherosclerosis fluctuated widely in contrast to the consistently low levels in controls.[7] Autopsy studies which reveal a higher incidence of severe atherosclerosis in obese people, confirm the metabolic origin of such atherosclerosis.[8]

As a result of these considerations, clinicians have treated patients with atherosclerosis or tendency towards such conditions with low-fat diets. While attempts have been made in that direction,[9, 13] achieving a low-cholesterol diet is more difficult and of less value than a low-fat diet. Most of the body cholesterol consists of a mixture of exogenous or dietary cholesterol and endogenous cholesterol of hepatic origin. Several workers have reported relief of angina pectoris with fat restriction in diet,[10, 11] while others have produced angina pectoris with high fat feedings.[12]

Significance of Bundle Branch Block

One of the first articles to stress the benign nature of atypical right bundle branch block appeared in 1934 and described five cases of atypical right bundle branch block, four of whom had no cardiac symptoms, the electrocardiograms remained unchanged over many years with the patients continuing asymptomatic.[14] There was little or no evidence of cardiovascular disease on routine physical examination.[15] In considering the etiology of bundle branch block, arteriosclerotic heart disease is the common etiological type. In a study of 452 cases of bundle branch block[16] either right or left, 31 were examples of benign bundle branch block and these were usually right; the bundle branch block was considered benign when it existed without evidence of organic heart disease. The benign type of bundle branch block was thought to be due to benign intercurrent infections. When there is coronary artery disease, the prognosis with

right bundle branch block is better than with left bundle branch block. Frequently, either condition is compatible with a long and useful life. Wolfran[17] also reported a considerable percentage of cases of bundle branch block unassociated with clinical heart disease; most of the blocks were of right bundle branch type. There are reported instances of benign bundle branch block in the same family.[18]

In contrast to instances of permanent bundle branch block, there have been a number of reports of transient bundle branch block. Transient bundle branch block due to myocardial changes secondary to heart failure has been reported[19] and other workers have reported transitory bundle branch block both in the presence and absence of organic heart disease.[20] Bishop[21] followed a case for nine years following an episode of transient left bundle branch block. Master reported the presence of transient bundle branch block during an attack of angina pectoris and he suggested that even with septal infarction, bundle branch block may be transitory until collateral circulation has taken place.[22] Kalett[23] reported a case of left bundle branch block which existed for four years following coronary occlusion and then disappeared spontaneously, the patient remaining symptom-free. This was unusual in that once established, such block is generally permanent.

COMMENT

While the exact pathogenesis has not been elucidated, recent studies indicate a close connection between the deposition of cholesterol within the lumen of coronary arteries and the process of atherosclerosis. What effect blood cholesterol levels have upon the deposition of cholesterol within the intima of coronary arteries and whether this process can be influenced by exogenous cholesterol is debatable. However, it is well known that lowering blood cholesterol levels by means of dietary restriction of fats, frequently causes xanthomatous skin lesions to decrease in size. While atheromatous lesions within the intima of arteries need not respond in the exact manner, there should be a similar effect.

The relief of angina pectoris is generally presumed to be related to improved collateral circulation.[5]

In the particular instance herein reported, the association between blood cholesterol levels, electrocardiographic changes indicating cardiac abnormalities and the anginal symptoms cannot be disregarded. While the relief of anginal symptoms and the reversion of the pattern of bundle branch block may have been coincidental, the close association of these factors together with a reduction in blood cholesterol and the decrease in size of xanthoma tuberosum lesions achieved by means of reduction in exogenous cholesterol and fats, would indicate a common etiological factor. In view of recent experimental studies associating atherosclerosis with cholesterol metabolism, this one case may be a lucid demonstration of such association.

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Pulmonary Sporotrichosis

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Routine intradermal sensitivity tests for histoplasmosis and coccidioidomycosis, and not infrequently serological examinations for these infections, have long been recognized as part of the work up of a patient hospitalized with a diagnosis of tuberculosis. Sporotrichum infection, however, is not ordinarily expected to become a problem in the differential diagnosis of pulmonary tuberculosis.[1] In contrast to histoplasmosis and coccidioidomycosis the occurrence of sporotrichosis as a disease of the lungs without cutaneous involvement is exceedingly rare.[2, 3, 8] Such is the subject of this report.

A 53 year old white man was admitted to the Veterans Administration Center, Wadsworth, Kansas, on November 9, 1955, with a history of "lung trouble" for the past five years, which had become worse during the past two years. He had to quit farming and cattle feeding because of dyspnea and cough.

A chest x-ray film was taken by the State Mobile Unit on October 14, 1955, which showed severe disease throughout the upper two-thirds of the left and the upper third of the right lung. Hospitalization was advised by his private physician.

He denied having had skin lesions for which he was specifically and repeatedly questioned. He had spent all his life near Milford, Kansas, except for a period of Military Service when he was stationed in Colorado (Colorado Springs and Golden).

FIGURE 1

FIGURE 2

Figure 1: Showing fibro-cavitary disease in the upper two-thirds of the left lung and fibrocaseous disease in the upper third of the right lung.—*Figure 2:* Showing a 4.5 cm. cavity in the upper rt. lung containing a fluid level and cavity in the left upper lung.

From the Veterans Administration Center.

He was thin and appeared chronically ill. Over the upper half of the left lung resonance was diminished, tactile and vocal fremitus were increased, and there were coarse rales and rhonchi. These were also present over the right mid lung posteriorly. The blood pressure was 128/72, temperature 98.4, pulse 76, admission weight 124 pounds compared with an average weight of 130 pounds. One to two ounces of mucopurulent, yellowish sputum daily were expectorated.

On July 1, 1942, a 70 millimeter military induction film showed no evidence of disease. On February 3, 1950, there was minimal fibrosis in the left apex, blunting of the costophrenic angles and thinning of the pulmonary markings consistent with emphysema. The next film on November 14, 1955, showed fibro-cavitary disease in the upper two-thirds of the left and fibrocaseous disease in the upper third of the right lung (Figure 1). A planigram on January 1, 1956, showed cavitation in the left and possible honey-combing in the mid portion of the right lung. Subsequently there was rapid bilateral progression of the disease until the film of March 7, 1956 (Figure 2), showed a 4.5 cm. cavity in the upper lobe of the right lung containing a fluid level as well as the previously seen cavity in the upper lobe of the left lung. X-ray film on April 6, 1956, showed regression for the first time which was more pronounced in the right lung (one month after the start of potassium iodide therapy). On October 25, 1956, a planigram of the left apex showed a 3 x 6 cm. cavity (Figure 3). No definite cavity was seen on a planigram through the right apex at this time.

There were no cutaneous or lymphatic lesions visible or palpable. Upper and lower GI series were negative. An x-ray survey of the lung bones of the upper and lower extremities was negative. Sigmoidoscopic examination was negative except for small benign polyps which were fulgurated.

Serological examinations for tularemia, brucellosis, typhoid, para-typhoid, and syphilis were negative. A complement fixation test for histoplasmosis performed in Furcolow's Laboratory (Kansas City Field Station, USPHS) was positive in January, 1956, with a titer of 1:8. A repeat test within eight weeks was negative. Intradermal sensitivity tests were negative using intermediate and second strength PPD, histoplasmin 1:500, coccidioidin 1:100, and blastomycin 1:100. Sixteen sputum cultures for acid fast bacilli were negative.

Twelve sputum cultures for fungi were positive for Sporotrichum. After five days of growth at 37°C, and after seven days of growth at room temperature, on brain heart infusion glucose blood agar, the typical yeast phase of Sporotrichum schenckii (Figure 4) was obtained. After 14 days of growth at room temperature on the same medium, the culture showed the yeast phase and mycelium formation at the edge of

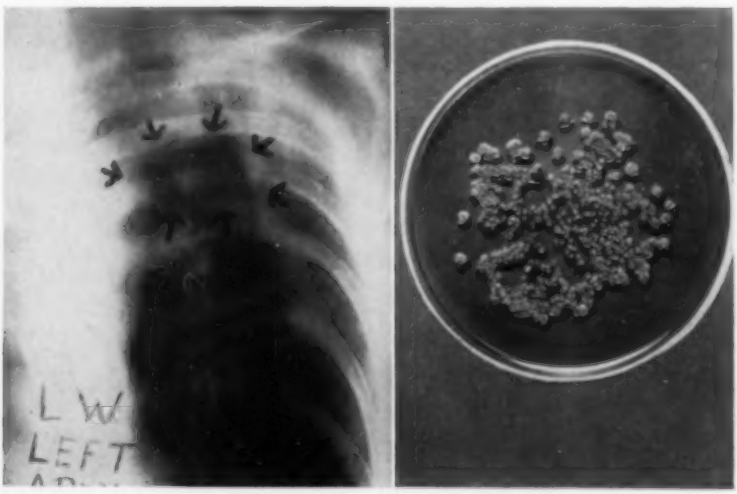

FIGURE 3 FIGURE 4

Figure 3: Showing a 3 x 6 cm. left cavity.—*Figure 4:* Showing the yeast phase of Sporotrichum schenckii.

the colony (Figure 5). An intraperitoneal mouse inoculation with one of the positive yeast phase cultures was positive for Sporotrichum schenckii (Figure 6). Identity of the organisms was confirmed by the Veterans Administration Area Reference Laboratory in St. Louis, Missouri. Serological examinations performed by Walter Reed Army Institute were reported as follows: Histoplasmin whole yeast phase antigen negative, blastomycin yeast phase positive with titer of 1:8, coccidioidin negative, sporotrichum yeast phase positive with titer of 1:64. Agglutination tests approximately two months apart were positive for sporotrichosis with a titer of 1:320 in Conant's Laboratory, Duke University School of Medicine. The cigar-shaped gram-positive bodies of Sporotrichum were also demonstrated on direct smears of sputum.

Bronchoscopy on March 5, 1956, showed no intrinsic bronchial lesions, but thick secretions were present in the left main bronchus. Examination of the washings for malignant cells was negative. A culture of the washings was sterile for acid fast bacilli and positive for Sporotrichum schenckii.

The Sporotrichum was cultured on media containing isoniazid and streptomycin to see whether the organisms would show a more abundant growth in the presence of these drugs. This was done because of the initial rapid spread of the disease during INH and PAS therapy. However, there was no noticeable difference in the growth on Thompson's medium (brain heart infusion glucose blood agar with 20 units of penicillin per milliliter and 40 units of streptomycin per milliliter).

After the initial positive sputum cultures for Sporotrichum were obtained, monthly cultures were performed. Except for negative cultures for sporotrichum in February and March of 1957, all other cultures, including the most recent one of June 1957, were positive.

Since the presumptive diagnosis on admission was pulmonary tuberculosis, chemotherapy was started on November 22, 1955, using INH 300 mg. daily and PAS 12 gms. daily. In addition 500,000 units of penicillin was given daily for six days and achromycin was given in a dosage of one gram daily for 17 days. Saturated solution of potassium iodide was started March 6, 1956, after sporotrichosis had been definitely diagnosed and tuberculosis ruled out. Isoniazid and PAS were discontinued. The dose of saturated solution of potassium iodide was gradually increased to 216 drops daily. Dihydroxystilbamadine was given intravenously during the early months of treatment concurrently with the administration of potassium iodide. A total dosage of 3,825 mgs. of dihydroxystilbamadine was given between April 20, 1956, and June 1, 1956. It was then discontinued because of unpleasant side reactions following the intravenous injections.[4]

FIGURE 5

FIGURE 6

Figure 5: Showing the yeast phase and mycelium formation at the edge of the colony after 14 days of growth.—*Figure 6:* Mesentery of a mouse inoculated with yeast phase culture, showing Sporotrichum schenckii. (Gram strain) (magnification 480X).

The weight remained stable at about 128 pounds between November 1955 and April 1956. However, between April 1956 and December 1956, there was a 21 pound weight gain from 128 to 149 pounds. During the first month of hospitalization the temperature varied from within normal limits to maximums of 99° F. A maximum of 100 was reached on two occasions. Subsequently there were occasional temperature elevations to 99° F. (July 1957).

Treatment with amphotericin B is contemplated in view of the fact that the treatment with potassium iodide failed to result in negative sputum cultures for Sporotrichum schenckii.

DISCUSSION

When sporotrichosis is diagnosed, it is usually found as a disease of the skin, mucous membranes, lymphatic tissues, viscera, or bones or any combination of these .[5] The usual port of entry for the fungus of sporotrichosis is a wound of the hand (this is a disease common in gardeners, for example) causing cutaneous lesions and from there the fungus can spread via the lymphatics and cause visceral involvement.

If the sputum harbors Sporotrichum, the latter can be demonstrated also by direct smear of the sputum. Our patient had a positive direct smear of the sputum for sporotrichum. Webster and Willander described recently a case of sporotrichosis of the knee in which the aspirate was positive for sporotrichosis on direct smear.[6]

Localized and disseminated forms of the disease have been recognized. Cases of cutaneous sporotrichosis with visceral manifestations, while not being frequent, are not rare.[7] Visceral involvement alone appears to be uncommon. Sporotrichosis localized to the lungs alone, without other visceral localization, is exceedingly rare. To the best of our knowledge we have been able to find, in the world literature, only nine cases of sporotrichosis limited to the lungs.[8]

There can be no doubt about the diagnosis of pulmonary sporotrichosis in the present case, since all Koch's postulates have been fulfilled.

Immunological procedures may be an aid in diagnosis. It is known that complement fixation methods between Histoplasma capsulatum, Blastomyces dermatitidis, Candida albicans, Coccidioides immitis give positive cross reactions.[9] There are also frequent positive cross reactions between histoplasmosis and blastomycosis. (Emmons and co-workers found that a dilution of 1:100 of histoplasmin gave a positive reaction in guinea pigs with blastomycosis, coccidioidomycosis and that, likewise, patients did react to both histoplasmin and blastomycin.[10]) Also positive cross reaction between Sporotrichum schenckii and several strains of pneumococci have been reported.[11]

Routine serological tests in our patient showed positive cross reaction between histoplasmosis and blastomycosis. The fact that the patient had a positive reaction for blastomycosis aroused our suspicion that he might harbor blastomycosis or any other fungus disease because of a possible cross reaction and a careful search for fungi, including sporotrichosis, was therefore made.

This case again exemplifies the fact that if a patient presents himself with an obscure lung condition an intensive search for sporotrichosis,

even if it is rare and unlikely to be found, should be included in the routine work up of the patient, because as D. T. Smith puts it: ". . . and from time to time the investigators will be rewarded with an unusual diagnosis—even a case of pulmonary sporotrichosis." [8]

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Editorial

Peace: A Task for the Medical World

In all primitive races the practice of medicine and the priesthood were closely related and the same person entrusted with both the interpretation and application of divine manifestations to the welfare of mankind. For this office the wisest of the tribe were chosen. To rule the tribe and to organize it for war, the bravest and most cunning rather than the most sensitive and intelligent were selected.

According to our current interpretation of primitive sociology we assume that the earliest human professions were Priest-Physician and Politician-Warrior. Attempts to explain the inscrutable mystery of Creation through metaphysical and philosophical reasoning gradually disclosed two roles in the search for truth and its application for the benefit of mankind: those of the true priest and the objective physician. The priest deciphers spiritual matters, judges deviations, and seeks healing or comfort by supernatural means. The physician searches the expression of the handiwork of the Creator, the ultimate truth, in the morphological and functional aspects of nature. By deduction and experimentation he seeks to understand the normal or healthy state of man and also the intrinsic and extrinsic factors and agents which produce the abnormal or diseased state. He dedicates his life to the prevention and cure of disease.

The objective of the clergy is to sustain the eminence of man on the basis of faith, the metaphysics of which is not within the comprehension of many and therefore must be supported by the incontestable pronouncements of dogma. The strong bonds of religion will unify great masses of people, the tenets of which however are not now, and perhaps never will be, amenable to objective reasoning.

The physician studies and serves the most valuable and perfect product of Creation: Man. Fundamentally identical in all the world, the differences in race or traits are insignificant when one considers genetic factors, structure and function. The common devotion to the welfare of mankind gives the medical profession a stamp of fraternity. In every country the physician finds colleagues who have the same basic interest in humanity and who pursue the common task of defending the life and health of others.

I have visited and lived in countries on five continents with inhabitants of many races having different degrees of progress, cultural traditions, economic conditions and religious beliefs. By this experience I have confirmed the extraordinary similarity of the attitude of one physician to another, of the physician to the community, and the community to the physician. The fundamental reason for this unity of spirit is that the brain and the heart, like all the cells of our functional system whether serving the basic vegetative functions or highly specialized to give each of us an individual character, are essentially the same for all human beings. This casts the physician in a privileged role, namely that of uniting

the people of the world for the most positive of all reasons; the conservation of life and health. Wars occur because of negative factors, dissimilarity in political or religious views and disagreement over the interplay of economic power. Atomic energy, a new and powerful tool, has recently become available to man. In the hands of some politicians who are enemies of freedom and human tolerance, it is a negative force jeopardizing the future of the human race. In the hands of the world's physicians, this same power has already become a significant positive factor for health and peace. Common ground to unite the world on a religious, political, or economic basis may never be found. Brotherhood is possible however, through worldwide interest in a unique positive factor; the preservation of man's most precious gift: Life. We physicians are by natural right the apostles of this campaign.

OVIDIO GARCIA-ROSELL, M.D., F.C.C.P.*
Lima, Peru

*Regent for Peru.

COLLEGE INTERIM SESSION AND SEMI-ANNUAL MEETING, BOARD OF REGENTS

The Interim Session of the College will be held in Rochester, Minnesota, November 29, 30 and the morning of December 1. Headquarters will be at the Kahler Hotel where round table luncheons will be held. The scientific sessions will take place in Plummer Hall and Mann Hall of the Mayo Clinic buildings. Fireside Conferences will be held in the Mayo Foundation House. There will also be tours of the Mayo Clinic, technical exhibits, examinations for Fellowship, dinner and dancing and four motion picture sessions. The Semi-Annual meeting of the Board of Regents and Board of Governors of the College will be held at the Hotel Radisson in Minneapolis, December 1. Following is the preliminary program for the meeting:

Saturday, November 29

Thoracic and Cardiovascular Surgical Clinics:

Methodist Hospital—O. Theron Clagett

St. Mary's Hospital—John W. Kirklin, D. C. McGoon

Pulmonary Section—Plummer Hall, 2:00 p.m.

Newer Developments in the Chemotherapy of Tuberculosis
Martin J. FitzPatrick, Kansas City, Kansas

Current Standards for Surgical Therapy of Tuberculosis
John B. Grow, Denver, Colorado

A Serologic Test for Diagnosis of Tuberculosis
Guy P. Youmans, Chicago, Illinois

Surgery of the Trachea and Bronchi
Donald L. Paulson, Dallas, Texas

Recent Developments in the Management of Fungous Diseases
Michael L. Furcolow, Kansas City, Kansas

Recent Evaluations of Sarcoidosis
Harold L. Israel, Philadelphia, Pennsylvania

Cardiac Section—Mann Hall, 2:00 p.m.

Clinical Manifestation of Several Types of Tricuspid Valvular Disease
Oglesby Paul, Chicago, Illinois

Femoral Artery Blood Flow
D. J. Ferguson, Minneapolis, Minnesota

Hypothermia for Intracardiac Surgery
F. John Lewis, Chicago, Illinois

Diagnostic Application of Indicator-Dilution Curves using a Central Sampling Technic
H. J. C. Swan, Rochester, Minnesota

Experience with Chlorothiazide in the Management of Hypertension
Robert L. Grissom, Omaha, Nebraska

Sunday, November 30

Optional tours of medical buildings in Rochester.

Round Table Luncheons

Disorders of Esophageal Motility
Moderator: Charles F. Code, Rochester, Minnesota

Bronchography, Indications and Techniques
Moderator: Sheldon E. Domm, Knoxville, Tennessee

Surgical Treatment of Acquired Valvular Heart Disease
Moderator: Robert P. Glover, Philadelphia, Pennsylvania

Early Detection of Emphysema
Moderator: Peter A. Theodos, Philadelphia, Pennsylvania

Scientific Session

Intrathoracic Complications of Subphrenic Infection
David P. Boyd, Boston, Massachusetts
Clinical Application of the Carbon Monoxide Method of Estimating Diffusion Capacity of the Lungs
David W. Cugell, Chicago, Illinois
Current Thoughts on Asthma
John M. Sheldon, Ann Arbor, Michigan
The Staphylococcus: 1959 Nemesis
Robert J. Anderson, Atlanta, Georgia
Current Concepts of Interstitial Pulmonary Fibrosis
Howard S. Van Ordstrand, Cleveland, Ohio

Fireside Conferences and Local Discussors

The Lung in Systemic Disease
F. E. Donoghue, Rochester
Pulmonary Function Tests and their Utilization
Ward S. Fowler, Rochester
Chemotherapy of Tuberculosis
David T. Carr, Rochester
Allergy in Pulmonary Diseases
Louis E. Prickman, Rochester
Carcinoma of the Lung
O. T. Clagett, Rochester
Pulmonary Hypertension
Howard B. Burchell, Rochester
Diagnostic and Surgical Methods in Intracardiac Septal Defect
R. O. Brandenburg, Rochester
Medical and Emotional Rehabilitation following Myocardial Infarction
Richard M. Steinhilber, Rochester
Techniques in Cardiac Diagnosis (Roentgenologic, catheterization, etc.)
Earl H. Wood, Rochester
Specific and Non-specific Therapeutic Approaches to Congestive Heart Failure
R. L. Parker, Rochester

Monday, December 1—Rochester—Mann Hall

Mayo Clinic Chest Conference—Diagnostic Problems
Herman J. Moersch, Rochester, Chairman
Cardiac Conference—Clinicopathologic Conference
J. E. Edwards, Rochester, Chairman
Thoracic and Cardiovascular Surgical Clinics
F. H. Ellis and P. E. Bernatz, Rochester

Minneapolis

Chartered buses will leave Rochester at 1:00 p.m. to arrive in Minneapolis in advance of the sessions to begin at 3:30 p.m.

Meeting, Board of Regents and Board of Governors

Dinner and panel discussion—"Inhalation Therapy"

Moderator: Edwin R. Levine, Chicago, Illinois

Panel: Seymour M. Farber, San Francisco, California; H. F. Helmholz, Rochester; William F. Miller, Dallas, Texas; Maurice S. Segal, Boston, Massachusetts

Dr. R. Drew Miller, Chairman, Pulmonary Section, and Dr. Raymond D. Pruitt, Chairman, Cardiac Section, Committee on Scientific Program for the Interim Session, have announced that the complete program will be published in the November issue of *Diseases of the Chest*. Physicians planning to attend the meetings are requested to write directly to the Kahler Hotel in Rochester and the Hotel Radisson in Minneapolis for reservations, giving arrival and departure dates. The Clinical Meeting of the American Medical Association will take place in Minneapolis, December 2-5.

College Chapter News

SOUTHERN CHAPTER

The 15th annual meeting of the Southern Chapter, comprised of the 16 southern states and the District of Columbia, will be held in conjunction with the meeting of the Louisiana Chapter, at the Jung Hotel, New Orleans, November 2 and 3. The following program will be presented:

Sunday, November 2—Morning Session

A. H. Russakoff, Birmingham, Alabama, presiding

9:25 a.m. Introductory remarks
Joseph S. Cruise, Atlanta, Georgia, President, Southern Chapter

9:30 a.m. "Roentgen Aspects of Active Histoplasmosis"
Earl E. Little, Jr., Little Rock, Arkansas

"Some Problems of Staphylococcal Pneumonia"
Charles A. Le Maistre, Atlanta, Georgia

"An Appraisal of the Clinical Value of Prolonged Positive Pressure Breathing"
Ben V. Branscomb, Birmingham, Alabama

"A Clinical Study of Chronic Pulmonary Disease due to Atypical Mycobacteria"
Albert G. Lewis, Jr., Tampa, Florida

"Pulmonary Fibrosis: A Histochemical Approach"
A. E. Anderson, Jr., Jacksonville, Florida

Afternoon Session

Robert R. Shaw, Dallas, Texas, presiding

2:00 p.m. "Respiratory Difficulties Associated with Anomalies of the Aortic Arch"
J. Walter Park, III, and Sam Greer, San Antonio, Texas

"Thoracic Surgical Conditions in Infants"
E. S. Crossett, El Paso, Texas

"The Problem of Persistent Positive Sputum after Resection for Pulmonary Tuberculosis"
Clyde Rush, Sanatorium, Texas

"Esophagodiverticulostomy for Stenosis of Upper Esophagus Associated with Zenker's Diverticulum"
Edward F. Skinner and Gene Page, Memphis, Tennessee

"Substitution Operation for Esophageal Strictures"
Osler A. Abbott, Atlanta, Georgia

"Surgical Treatment of Bronchogenic Carcinoma"
G. V. Brindley, Jr., Temple, Texas

6:00 p.m. Cocktail party

Monday, November 3—Morning Session

Frank W. Pickell, Baton Rouge, Louisiana, Louisiana Chapter President, presiding

8:55 a.m. Introduction of Daniel E. Jenkins, Houston, Texas, First Vice President, Southern Chapter

9:00 a.m. "Cardiovascular Research in Britain and in Russia"
T. J. Reeves, Birmingham, Alabama

"Problems in Diagnosis and Treatment of Patent Ductus Arteriosus"
Robert G. Ellison, Augusta, Georgia

"Metabolism of the Isolated Heart"
Watts R. Webb and S. S. Lee, Jackson, Mississippi

"Experiences in the Surgical Management of Tumors of the Chest Wall"
Harold C. Spear, DeWitt C. Daughtry, and John G. Chesney, Miami, Florida

Fifth Annual Paul Turner Memorial Lecture—"Bronchogenic Carcinoma"
Alton Ochsner, New Orleans, Louisiana

Afternoon Session

2:00 p.m. Symposium: "What Do the Newer Research Tools in Cardiovascular Disease Hold for Future Application?"
Moderator: George E. Burch, New Orleans, Louisiana

Ballistocardiography and Kinetocardiography
E. E. Eddleman, Birmingham, Alabama

Left Heart Catheterization
T. J. Reeves, Birmingham, Alabama

Electrocardiography and Kinetocardiography
Manuel Gardberg, New Orleans, Louisiana

POTOMAC CHAPTER

The Potomac Chapter, representing Maryland, West Virginia, and the District of Columbia, will present its annual meeting at the Statler Hilton Hotel, Washington, D.C. on November 23. The following program will be presented:

Roy G. Klepser, Washington, D.C., chapter president, presiding

8:45 a.m. Registration

9:15 a.m. Business Meeting

9:30 a.m. Symposium: "Staphylococcal Pneumonia and its Complications"
Moderator: Milton Gusack, Washington, D.C.

Clinical and Radiographic Aspects
Joseph M. Lo Presti, Washington, D.C.

Surgical Implications
Edgar W. Davis, Washington, D.C.

Symposium: "Current Controversies in Pulmonary Tuberculosis—The Duration of Chemotherapy; Problems of Bacterial Resistance and Relapse; The Question of Early Surgery; Management of the 'Open Negative'"
Moderator: Sol Katz, Washington, D.C.

Panel: Oscar Auerbach, East Orange, New Jersey; J. Maxwell Chamberlain, New York City; Richard F. Kieffer, Baltimore, Maryland; James W. Raleigh, Sunmount, New York

12:00 noon Round table luncheon panels:
A) "Which Antibiotic?: Factors Influencing One's Choice"
Moderator: John P. Utz, Bethesda, Maryland
B) "Anesthetic Problems in Cardiac Surgery"
Moderator: Charles E. Fierst, Washington, D.C.
C) "Bronchial Carcinoma: Preventable? Treatable?"
Moderator: Oscar Auerbach, East Orange, New Jersey

Afternoon session—Cardiovascular Seminar

William L. Cooke, Charleston, West Virginia, Vice President, presiding

1:00 p.m. "Unusual Causes of Heart Failure"
Thomas W. Mattingly, Washington, D.C.

Symposium: "Diagnostic Methods in the Study of Circulatory Shunts"
Moderator: Andrew G. Morrow, Bethesda, Maryland

Panel: Eugene Braunwald, Robert Frye, and Robert Long, Bethesda, Maryland

Fireside Conferences

"Coronary Artery Disease"
Benjamin Manchester, Washington, D.C.

"Emphysema"
James P. Mann, Washington, D.C.

"Esophageal Diseases"
Morris H. O'Dell, Charleston, West Virginia

"Clues and Red Herrings in Congenital Heart Disease"
Bernard J. Walsh, Washington, D.C.

MINNESOTA CHAPTER

Newly elected officers of the Minnesota Chapter are:

President:	J. Paul Medelman, St. Paul
Vice-President:	Sumner S. Cohen, Oak Terrace
Secretary-Treasurer:	Coleman B. Connolly, St. Paul

VIRGINIA CHAPTER

The annual meeting of the Virginia Chapter will be held on Sunday, October 12 in the Flemish Room of the Jefferson Hotel, Richmond, Virginia.

PACIFIC NORTHWEST CHAPTER

The Willow Chest Centre, Vancouver, British Columbia, will be the location for the annual meeting of the Pacific Northwest Chapter, November 7-8.

RIO GRANDE DO SUL CHAPTER

In cooperation with the Tuberculosis Society of Rio Grande do Sul and the Liga Rio Grandense Contra a Tuberculose, the Rio Grande do Sul Chapter of the College celebrated "Tuberculosis Week" in Porto Alegre on May 17. Professor Carlos Bento, Governor for the College, presided at the opening session held in the Governor's Palace, and spoke on the activities of the three organizations. Professor Bento also represented the College at the dedication ceremonies of a new rehabilitation center for tuberculosis patients at the Hospital do Partenon.

ANNOUNCEMENTS

The Southern Thoracic Surgical Association will hold its annual meeting at the Deauville Hotel, Miami Beach, Florida, November 28-30, 1958.

The School for Inhalation Therapists of St. Elizabeth Hospital, Elizabeth, New Jersey, announces the beginning of its Second Academic Sessions on October 14. The course will consist of lectures and demonstrations two mornings each week for six months. Further information may be obtained by writing to: Dr. Burton M. Cohen, c/o Mr. B. R. Rosa, Supervisor, Inhalation Therapy Service, St. Elizabeth's Hospital, Elizabeth, New Jersey.

MEDICAL SERVICE BUREAU

POSITION WANTED

Residency-trained chest clinician seeks directorship of small chest hospital or chest service unit of hospital. Background includes 10 years full-time department head of chest and bronchoscopic services of large county institution; broad administrative experience; F.C.C.P., F.A.C.S. Please address inquiries to Box 301B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Full-time chest physicians wanted for positions in state mental hospitals in a midwestern state. Assignments include diagnosis, therapy and research. Salaries range from $7200 to $20,000 per year, depending upon position, education and experience. Nominal deduction for maintenance. Civil Service, liberal pension plan, sick leave, annual paid vacation. Requirements: graduation from an approved medical school and one year rotating internship. Training in chest diseases. Please address inquiries to Box 298A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Staff or resident physician wanted for 130-bed accredited tuberculosis hospital. Must have or obtain Indiana license. Salary $500 per month or more, depending upon qualifications. Family maintenance, three bedrooms, two baths, garage, food, laundry, Social Security, pension plan. Apply: Director, Healthwin Hospital, South Bend, Indiana.

Physician wanted for approved residency in tuberculosis. Accredited bi-county hospital, 219 beds pulmonary diseases, 30 beds rehabilitation chronic illness. Starting salary $600 monthly, includes furnished modern house for family. Must be eligible for California license. Write: Medical Director, Tulare-Kings Counties Hospital, Springville, California.

Residency in pulmonary diseases available immediately at Baylor University College of Medicine, Houston, Texas. Opportunity for training in endoscopy, pulmonary physiology, tuberculosis and non-tuberculous diseases of the chest. One or more years residency in Internal Medicine desirable. Address inquiries to: Daniel E. Jenkins, M.D., Department of Medicine, Baylor University College of Medicine, Houston, Texas.

Assistant medical director wanted for 110-bed tuberculosis hospital. Salary $9,000 per year plus complete family maintenance including apartment, food, laundry, and utilities. Apply: Executive Director, State Tuberculosis Hospital Commission, New Capitol Annex, Frankfort, Kentucky.

CALENDAR OF EVENTS

NATIONAL MEETING

Interim Session

American College of Chest Physicians
Rochester, Minnesota, November 29-30, 1958

Semi-annual Meeting, Board of Regents
American College of Chest Physicians
Minneapolis, Minnesota, December 1, 1958

POSTGRADUATE COURSES

13th Annual Course, "Clinical Cardiopulmonary Physiology"
Chicago, Illinois, October 13-17, 1958

11th Annual Course on Diseases of the Chest
New York City, November 10-14, 1958

CHAPTER MEETINGS

Virginia Chapter, Richmond, October 12
Colorado Chapter, Denver, October 15
Southern Chapter, New Orleans, November 2-3
Pacific Northwest Chapter, Vancouver, B.C., November 7-8
Potomac Chapter, Washington, D.C., November 23

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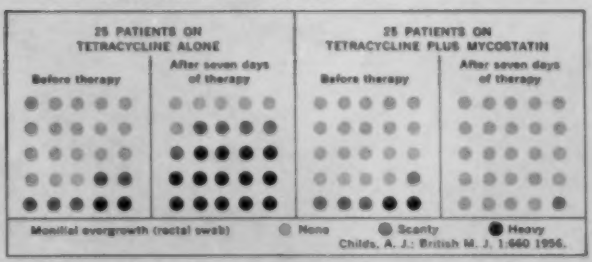

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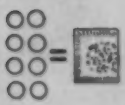

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